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RUI EDUARDO ARANTES DE PASSOS SOUSA

4 ANOS DE EXPERIÊNCIA PROFISSIONAL COMO GESTOR DE ASSUNTOS MÉDICOS

4 YEARS PROFESSIONAL EXPERIENCE AS A MEDICAL AFFAIRS MANAGER

Relatório de formação durante o exercício profissional, apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica do Doutor Luís Almeida, Professor Associado Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

On-the-job training report presented to the University of Aveiro to fulfill the requirements for the degree of Master in Pharmaceutical Biomedicine, conducted under the scientific guidance of Doctor Luís Almeida, Guest Associate Professor of the Autonomous Section of Health Sciences, University of Aveiro.

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Palavras-chave Gestor de Assuntos Médicos, Companhia Farmacêutica, Formação, Experiência Profissional

Resumo

Nos últimos anos, os departamentos de Assuntos Médicos assumiram um importante papel estratégico nas companhias farmacêuticas e de biotecnologia. Em resposta a um aumento da regulamentação e de exigência de transparência, os departamentos de Assuntos Médicos mudaram o seu foco do apoio às atividades comerciais e de marketing para as responsabilidades na interface com os líderes de opinião, para o desenvolvimento médico, para as comunicações científicas e para outras tarefas médicas emergentes. Durante os quatro anos de experiência profissional como Gestor de Assuntos Médicos tive a oportunidade de desempenhar um conjunto alargado de tarefas que me permitiram desenvolver uma formação sólida, adquirindo ou reforçando competências fulcrais nesta área. Durante trinta e quatro meses trabalhei como Gestor de Assuntos Médicos para a área do Sistema Nervoso Central proporcionando um apoio mais direto às atividades de Marketing, Regulamentares e de Farmacovigilância. Nos últimos treze meses, após me ter tornado Gestor de Assuntos Médicos Internacional, assumi igualmente responsabilidades relacionadas com o desenvolvimento clínico de Fase IV, a gestão das comunicações científicas e escrita médica, a implementação de análises *post-hoc* e o apoio às atividades de Marketing global. Tive sempre como finalidade o alcançar da excelência no desempenho das tarefas sob minha responsabilidade, simultaneamente cumprindo os mais elevados padrões de ética e deontologia. Através do meu trabalho dedicado contribuí para o sucesso da minha companhia e, ao mesmo tempo, para a melhoria da saúde e do bem-estar de doentes e populações.

Keywords Medical Affairs Manager, Pharmaceutical Companies, Training, Professional Experience

Abstract

In recent years, medical affairs departments have taken on an important strategic role within pharmaceutical and biotechnology companies. In a response to the increased regulations and calls for transparency, medical affairs have shifted their focus away from commercial and marketing support to key opinion leaders interfacing responsibilities, medical advancement and medical communications activities as well as other emerging medical tasks. In my four years professional experience as a Medical Affairs Manager I have performed a wide variety of tasks that allowed me to develop a solid training, acquiring or strengthening core skills and competencies in this field. During thirty-four months I have worked as a Central Nervous System Medical Affairs Manager providing a more direct support to marketing, regulatory and pharmacovigilance activities. In the last thirteen months, after becoming International Medical Affairs Manager, I also took responsibilities related to phase IV clinical development, scientific communication management and medical writing, post-hoc analysis and global marketing support. I have always aimed at excellence while performing the activities under my responsibility, simultaneously attaining the highest professional and ethics standards. Through my devoted work I have positively contributed to the success of my company while contributing to the improvement of health and well-being of patients and populations.

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List of Abbreviations

Bial, Bial – Portela & Cª. S.A.

CNS, Central Nervous System

CTA, Clinical Trial Application

FTE, Full Time Equivalents

IIS, Investigator Initiated Study

IND, Investigational New Drug Application

KOL, Key Opinion Leaders

MAA, Marketing Authorisation Application

MSL, Medical Scientific Liaisons

NDA, New Drug Application

R&D, Research and Development

US, United States of America

1. The role of the medical affairs manager in a pharmaceutical company

Before describing my experience as a medical affairs manager it is important to define the key responsibilities and describe the main tasks usually attributed to these professionals in a pharmaceutical company. For a better understanding of the medical affairs role, the structure and organization of modern medical affairs departments will also be presented.

1.1 Key responsibilities of modern medical affairs managers

The common objective of all pharmaceutical companies is to discover, develop and market safe, efficacious and cost-effective medicines that will bring benefits to patients, health care professionals and consumers, and result in profitable returns to the company. In this process it is important that, at all stages in the life cycle of a pharmaceutical product, the needs and interests of those who will receive these medicines be paramount. It is consensually accepted that medical doctors with advanced training in pharmaceutical medicine are specially prepared to ensure this goal, as they are qualified not only to provide medical expertise but also, through the tradition of the Hippocratic Oath, to represent the needs and interests of patients (1).

Although (as will be detailed in section 1.3) each company may organize its medical affairs department differently, depending on the size and culture of the organization among other variables, this department's major areas of responsibility may be defined as:

- Act as the medical conscience of the company;
- Ensure adherence to relevant legal requirements and guidelines;
- Provide a medical perspective to product development;
- Provide the medical input to the servicing and support of marketed products throughout their life cycle;
- Provide general as well as specialised medical expertise, as required; and
- Act as the company's expert interface with all sectors of the medical profession as well as other external stakeholders (such as regulatory authorities, press and health technology assessment bodies) (1).

In a more operational description, medical affairs managers are usually responsible for:

- Accurate and appropriate communication of drug- and disease-specific information to internal and external customers;
- Conduction of late-phase post-marketing studies and pharmacoeconomic studies;
- Collection and reporting of adverse events and other support to pharmacovigilance activities;
- Implementation of educational programs;
- Support of product launch, including promotional materials review and approval;
- Scientific congress support; and
- Peer-reviewed publications management (2).

In summary, the ultimate goals of any medical affairs groups is to generate, package and disseminate medical and clinical information, while being compliant with the highest standards of ethics and applicable regulations (3).

Looking to these key responsibilities and goals, some points merit to be highlighted.

Firstly, medical affairs managers should always have as their first aim the overall improvement of health and well-being of patients and populations that may potentially use the marketed drugs under their responsibility. Nevertheless, to be effective, medical managers have to recognise both the clinical needs of patients and the commercial needs of the company. Although medical affairs managers work in close cooperation with marketing and sales teams and, ultimately, also have the objective of making the company profitable, this can only be achieved by attaining the highest standards of ethics and regulatory obligations.

At the first glance this may not seem feasible as the interests of marketing/sales and medical affairs departments may look contradictory but at a closer look this is far from true. In fact, we are faced with a potential win-win situation. The best way to boost sales of any given drug available in the market is to ensure its proper use, through the dissemination of all the available evidence to health care providers, minimizing all the potentials situations of misuse. The best marketing that may ever exist is the positive feedback of a patient to his doctor and, on the contrary, a sustained negative feedback will definitely impair further prescriptions. Being so, medical and marketing teams should work together to ensure a perfect alignment between available evidence and strategic

marketing while keeping the functional independence inside the organization, which is a key driver to ensure that medical affairs decisions are not commercially biased.

Not surprisingly, the recognition of the increasing importance of scientific communication is revealed by the decreasing number of sales representatives and increasing number of medical scientific liaisons (MSL) (4). This last group of professionals has on average a higher scientific background which allows them to much better implement the above mentioned win-win strategy. They are empowered to better communicate drug information to physicians and the better a given physician knows a drug, the better he will know how to use it and the better he will treat his patients, improving their conditions and at the same time minimising adverse events and potentially harmful drug-drug interactions. This will ultimately lead to a positive feedback that will increase prescriptions and, at the same time, contribute to overall health improvement of populations.

Secondly, it is clear from their roles that, to work effectively, medical affairs managers need to interact not only with other members of their department but also with colleagues in other departments, such as commercial, legal and communications ones, as well as with external stakeholders (1). In other words, through their support to different internal departments, medical affairs managers are at the centre of cross-functional teams inside the company. At the same time, they have an increasingly important role as the external face of the company in its interactions with stakeholders in the health care marketplace and other public and governmental bodies (Figure 1).

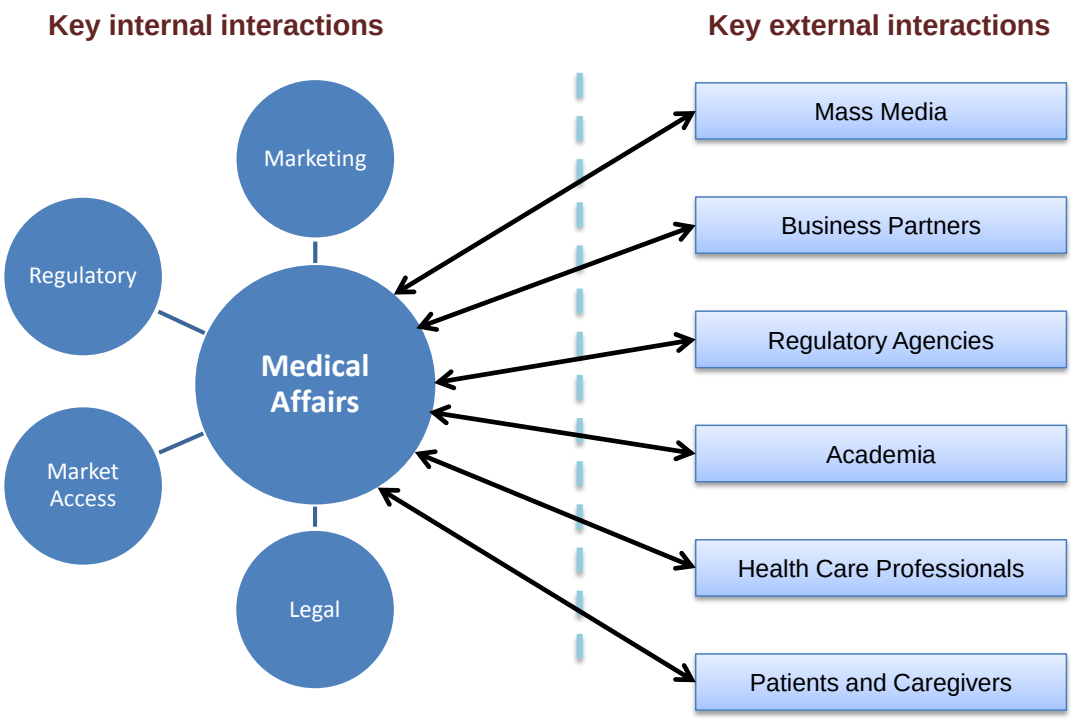

Figure 1. Medical Affairs Managers are at the interface with external stakeholders and at the core of internal cross-functional teams.

Thirdly, in a modern pharmaceutical company, members of the medical affairs department can expect to have an important role at all stages in a product's life cycle. Working with new product development colleagues from the earliest planning stages, their specialist skills and expertise help the team to drive the development process down the right path from the initial clinical development to product marketing and beyond (1).

Classically, medical affairs managers' responsibilities started before product approval by preparing the product launch regarding phase 4 studies, working with clinical research and other research groups on monographs and publication needs, creating standardized medical letters and enquiries, collecting adverse events, and developing educational programming, all of which continues throughout the years of marketing the product (Figure 2) (2).

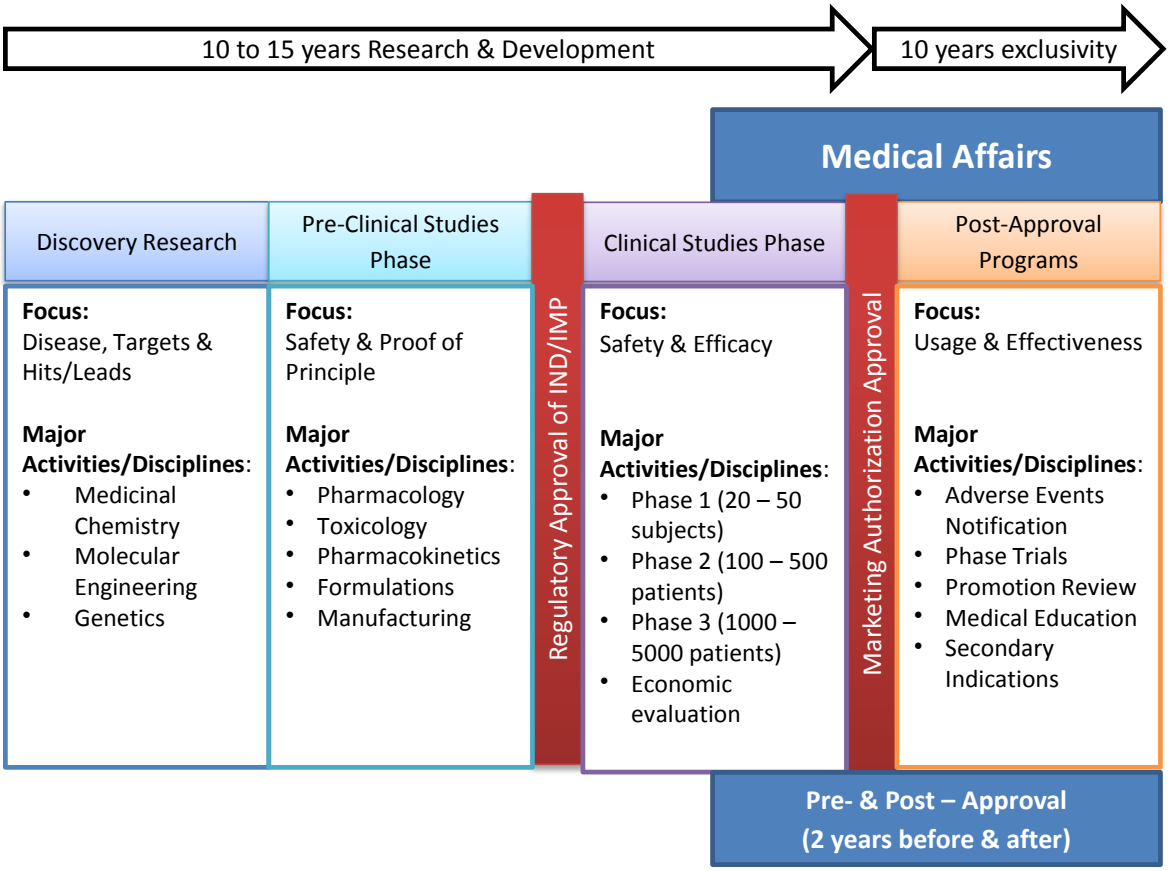

Figure 2. The classical role of medical affairs managers in the clinical development process (adapted) (2).

More recently, due to their expertise in the therapeutic area, their in depth knowledge of the unmet medical needs and their privileged position at the interface with key opinion leaders (KOL), medical affairs managers are being more and more frequently involved in the interpretation of the findings of phase 1 and phase 2 trials, actively participating with their advice in “go/no-go” decisions regarding the clinical development of pipeline drugs.

Despite this trend to the early involvement in the life cycle of a drug, the ideal time for medical affairs to begin and discontinue working with a drug is not yet consensual, in particular the timing for initiation.

In a recent survey to pharmaceutical companies, respondents mentioned that the time to start working with a brand would ideally be decided on a case-by-case basis but when asked to choose a stage, answers were considerable heterogeneous (Figure 3) (3).

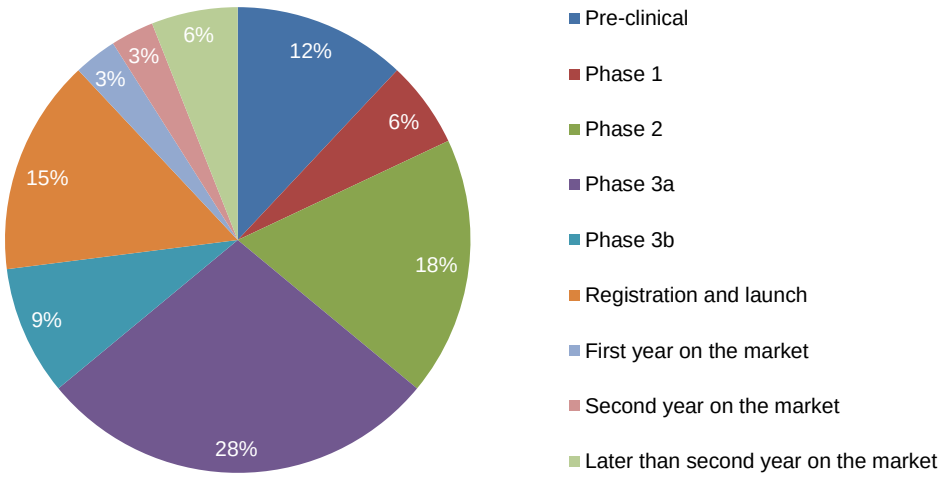

Figure 3. Stage when medical affairs departments start work with a new drug or drug candidate (adapted) (3).

Phase 3 is yet the main stage where medical affairs start work with a new drug (37% of the cases if we sum up phase 3a with 3b), with no other stage in the product lifecycle earning more than 20% of surveys responses (3).

In another study, where the timing for individuals activities were analysed, it was clear that certain medical affairs activities typically begin before phase 3. For instance, 70% of survey respondents initiated thought leader work on a brand between pre-clinical and phase 2. This is a good example why starting early should be a goal of every medical affairs department: the sooner members of the scientific and medical community are brought in to advise on drug development, the more prepared management will be when making strategic go/no-go decisions (3).

The stage at which medical affairs stop working with a medicinal product received a much more consensual response as 76% of surveyed pharmaceutical companies reported medical affairs never stop to work with the drug (Figure 4) (3).

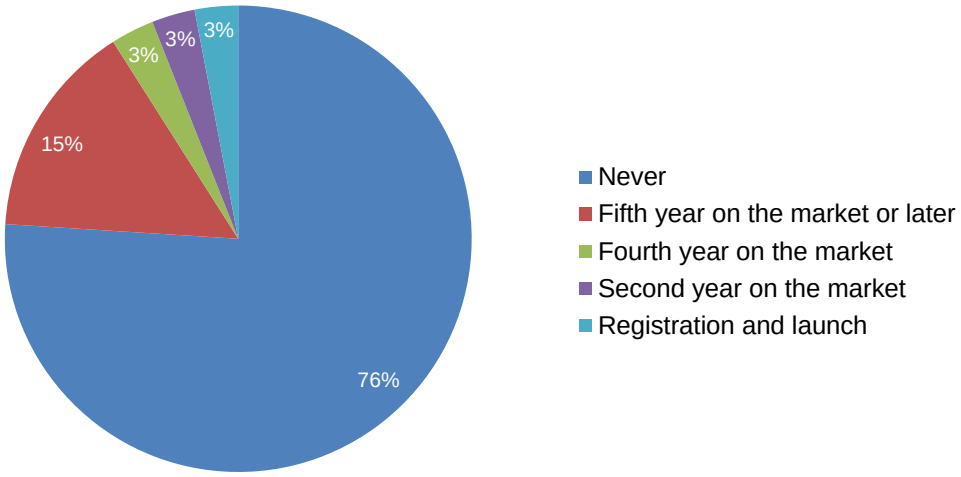

Figure 4. Stage when medical affairs departments stop work with a drug (adapted) (3).

It should be noted that although medical affairs work is never completed this does not mean that efforts are equally balanced throughout the entire life cycle, as different sub-functions have different roles at different stages. For instance, medical affairs having medical information responsibilities will continue to handle physician enquiries even after drugs lose patent protection but other areas such as though leader development or pharmacoeconomics probably will not be developed at those late stages. Overall, the amount of work and efforts tends to be lower as the life cycle progresses.

The importance of medical affairs in the life cycle management of a drug will expectedly growth as, in the future, it is likely that post-marketing studies will gain increasingly more importance, becoming a critical path in the clinical development of new drugs. In the proposed “in-life testing model” a company will begin by defining the minimum amount and kind of information it needs to secure approval for “in-life testing” of a new medicine. It will then perform a series of small, highly targeted clinical studies, using simulation, modelling and other technologies, to ensure that the product’s effectiveness and safety are understood, before submitting data to the relevant regulatory agency (thereby rendering the traditional four-phase approach to clinical development redundant). If the regulator is satisfied with the evidence, it will issue a “live license” permitting the company to market the medicine on a very restricted basis. The company will thereafter conduct “in-life testing” of that medicine in a small population of patients. With each substantive increase in evidence of the medicine’s safety and effectiveness, the regulator will extend

the license to cover a larger number of patients, a different patient population or multiple indications. The medicines which receive approval on a real-time basis will have live licenses contingent on the performance of extensive in-life testing, including studies in specific patient subpopulations, and a predetermined schedule for reviewing each set of results. If "in-life testing" confirms that a medicine is safe and effective, the company making will be granted an extended license or special permit so it will have an incentive to conduct further studies. In other words, the medicine on the market will have a prearranged, fully automated pathway throughout its life-cycle, and its development will be a continuous process rather than ending when it is approved (Figure 5). (5)

In this new "in life testing/live-licensing" model, medical affairs managers will expectedly actively participate in almost every step of the process as they are among the most well prepared professionals to implement this new proposed paradigm of clinical development (and market access) which is much closer to the current post-marketing studies than to the phase III clinical trials.

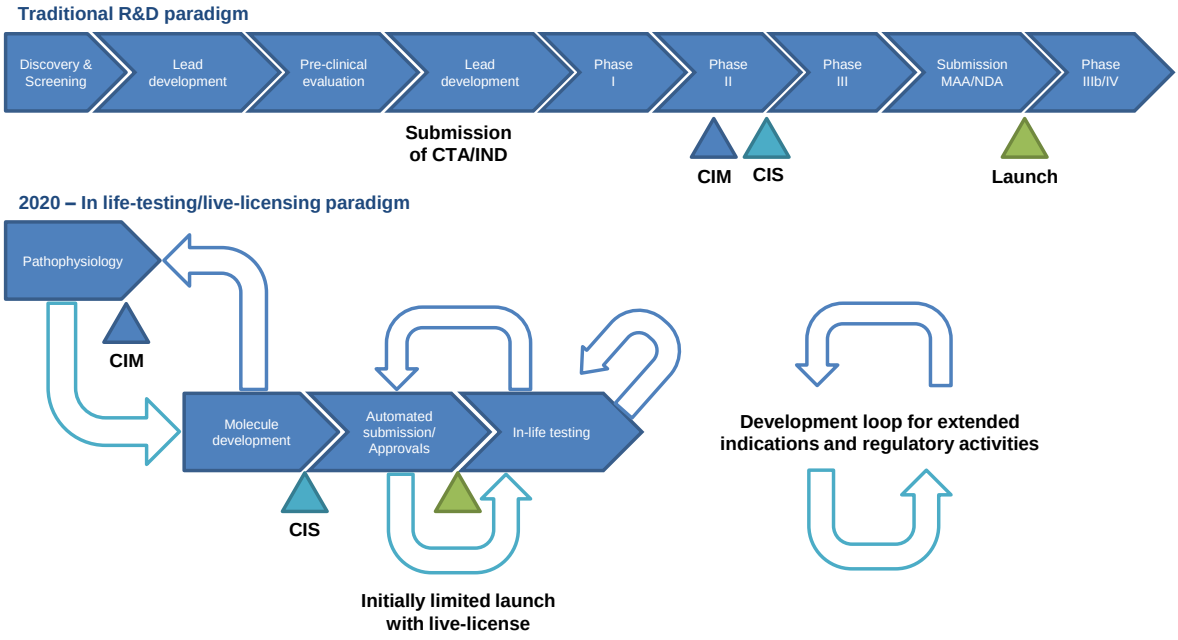

Figure 5. The medical affairs manager will expectedly gain a more predominant role in clinical development when research & development and regulation will be fully integrated and continuous (adapted) (5). CTA, Clinical Trial Application; IND, Investigational New Drug Application; CMI, confidence in mechanism; CIS, confidence in safety; MAA, Marketing Authorisation Application; NDA, New Drug Application.

In summary, an effective medical affairs manager contributes to the commercial success of the company while maintaining the highest professional and ethical standards, which can only be achieved ensuring that the right patients are making the best use of the marketed drugs, by contributing to the screening and optimized development of the best therapeutic medicinal products and by ensuring the most streamlined market access of new compounds.

1.2 Main activities developed in modern medical affairs departments

By fulfilling the responsibilities above mentioned, in recent years medical affairs departments have taken on an important strategic role within pharmaceutical and biotechnology companies. In a response to the increased regulations and calls for transparency, medical affairs have shifted their focus away from commercial and marketing support to KOL interfacing responsibilities, medical advancement and medical communications activities as well as other emerging medical tasks (3).

The main activities developed by medical affairs groups are schematically presented in Figure 6 and will be briefly detailed in this section.

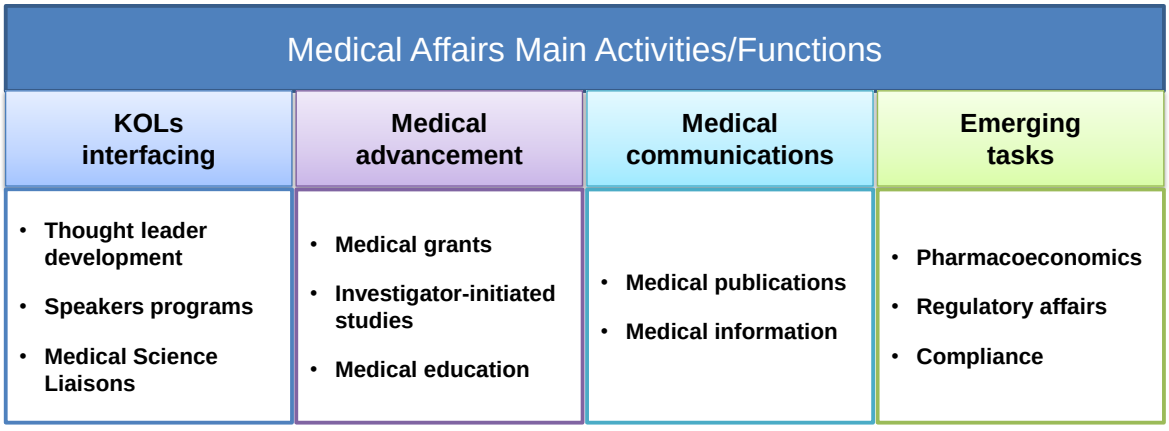

Figure 6. Main activities/functions developed in medical affairs departments. Although marketing support is still an activity developed by medical affairs departments it is no longer considered one of the main focus and much of the work is now included under medical education and compliance activities.

Although for didactic purposes these activities are presented in separate boxes they are not totally independent and there are strong connections between some of them.

Likewise, the same medical affairs manager may be responsible for just one, several, or all the activities, depending on how the medical affairs department is organized.

1.2.1 KOL interfacing

The interface of medical affairs with KOL encompass three major connections – thought leader development, speakers programs and MSL – that all together promote education and scientific communication.

We have mentioned before that sales model paradigm is being shifted, driven by new regulations, and it is now more based on scientific communication and education. As a result, interactions with KOL, while always critical, have grown in importance over the past years, as these physicians, if properly trained and educated, are at a privileged position to allow for a much faster spreading of the available scientific evidence which will ultimately lead to a faster and more rationale use of a new drug. Equally important, the feedback from these KOL is critical for the future development of the drug, pointing out areas where more evidence is needed or providing new insights and interpretations on available data.

Like most medical affairs activities, ***thought leader development*** starts with education. Successful pharmaceutical companies build thought leader relationships by sharing new, valuable information about medicines and the science behind them. When KOL receive education and training from pharmaceutical companies they become partners in science. KOL give back by participating in advisory panels for drug development or speak at international congresses. The entire medical community benefits when pharmaceutical companies foster a two-way street of scientific communication with thought leaders (3).

The relationship between pharmaceutical companies and thought leaders needs to be absolutely transparent to ensure this bidirectional flux of scientific communication is not commercially biased but strictly based on the best informed opinions.

Traditionally, a selected groups of KOL that were previously developed as experts in the product were invited to ***speakers programs***. Basically, those KOL would act on behalf of the companies in scientific events and lectures, helping to spread to the medical community the available evidence. As more and more transparency is required in this relation between pharmaceutical companies and KOL, full disclosure of payments received by KOL to perform this role is being made obligatory and, as consequence, KOL are refusing to participate in speakers programs feeling they may jeopardize their

credibility if they continue doing it. One interesting solution to this potential lack of speakers may be found inside house. As medical affairs managers are being involved at earlier stages of drug development they profit from an intense training in the field which is complemented by the close scientific bi-directional relationship with KOL. Ultimately, when the drug is launched they have both the knowledge and the respect from the scientific community that allows them to play the role of speakers, in many circumstances with even more success than the one that could be achieved by external speakers.

MSL serve as formal physician contact points, and they are not only responsible for disseminating medical relevant information but also for communicating current and potential opportunities to work with the company. They play this role not only with KOL but also with other physicians, playing now a critical role in the new paradigm of medical education as the key driver for drug growth in the market.

To be successful MSL need to have a solid background training and expertise in the field and always act in compliance with ethics and deontological obligations. Extreme caution should be taken to avoid a potential misinterpretation of MSL role, always making it clear that it is completely diverse from the one of sales representatives.

1.2.2 Medical advancement funding

A central function of medical affairs departments is to advance drug therapies as well as awareness of different diseases and their treatment options. Medical advancement funding is at the heart of the modern medical affairs department. This group of activities consists of medical grants, investigator-initiated trials and medical education. Each of these interconnected activities serves a vital role in promoting scientific knowledge and advancing new therapies (3).

Medical grants serve a vital role within medical advancement funding by functioning as the gateway to conducting investigator-initiated trials. Because of the plethora of proposed studies, with implications for off-label uses, line extensions and new therapies, medical affairs departments have had to streamline medical grant application and evaluation processes in order to remain aligned with their own strategic objectives. Furthermore, new regulations drive changes as companies adjust compliance. For example, sales representatives and MSL no longer play a role in the grant process. In an effort to

streamline medical grant processes, many companies have established guidelines and selection criteria to use when considering different grant proposals (3).

Investigator-initiated studies (IIS) provide opportunities for companies to explore applications for their drugs as well as its scientific understanding. In particular, IIS allow companies to meet their strategic goals via investigators' desire to expand on existing clinical data. Work performed by investigators offers a means to build a drug's body of publications, to develop thought leader relationships and potentially to expand indications through the exploration of new ideas (3).

IIS management has become more centralized, allowing drug companies to control the direction of trials by managing what studies are conducted and ensuring they are aligned with the overall development of the drug.

Like many activities within medical affairs in recent years, ***medical education*** has changed due to evolving regulations, and now, all external medical education activities can no longer be associated with commercial divisions due to potential biases. Therefore, companies restructured medical education and put up a firewall between medical education and marketing. Nevertheless, medical education activities will continue to play a role in medical affairs activities as they are supportive of other tasks such as thought leader development and also because pharmaceutical companies have a critical role in the medical education efforts of the community.

Included under medical education activities, medical affairs managers continue to have the responsibility to provide training to internal stakeholders (such as marketing, sales, regulatory or legal departments) in key therapeutic areas and product information, ensuring they have the necessary knowledge to perform their roles effectively and in a compliant way.

1.2.3 Medical communications

Medical communications includes two different sets of activities: medical publications, which is related with medical writing and publications, and medical information that consists in addressing inbound inquiries concerning scientific data, product labels and more. Each of these two main activities serves a significant role for medical affairs functions.

Medical affairs managers responsible for ***medical publications*** meet the duty and need that pharmaceutical companies have to communicate their scientific findings, results and trials to physicians, patients, pharmacists and payers. Companies disclose this information in a number of ways, but two of the most frequent and effective ones are international scientific congresses activities (posters or oral communications) and full-papers publications in peer-reviewed indexed journals.

Medical information activities are also critical for medical affairs managers. By properly addressing unsolicited medical questions, they help to maintain the best usage of the drug by clarifying all doubts, triaging potential safety issues (such as off-label use, adverse events or overdosage), as well as any potential quality problem. Medical information may be indirectly considered a component of medical education and it is another example where high level scientific training is required for a successful performance.

1.2.4 Emerging tasks

More pharmaceutical companies are bringing functions like compliance, health economics and regulatory affairs under the purview of medical affairs. This is an emerging trend and, in a recent survey, only the most forward-thinking companies have created solid reporting lines from each of these functions to medical affairs (Figure 7) (3).

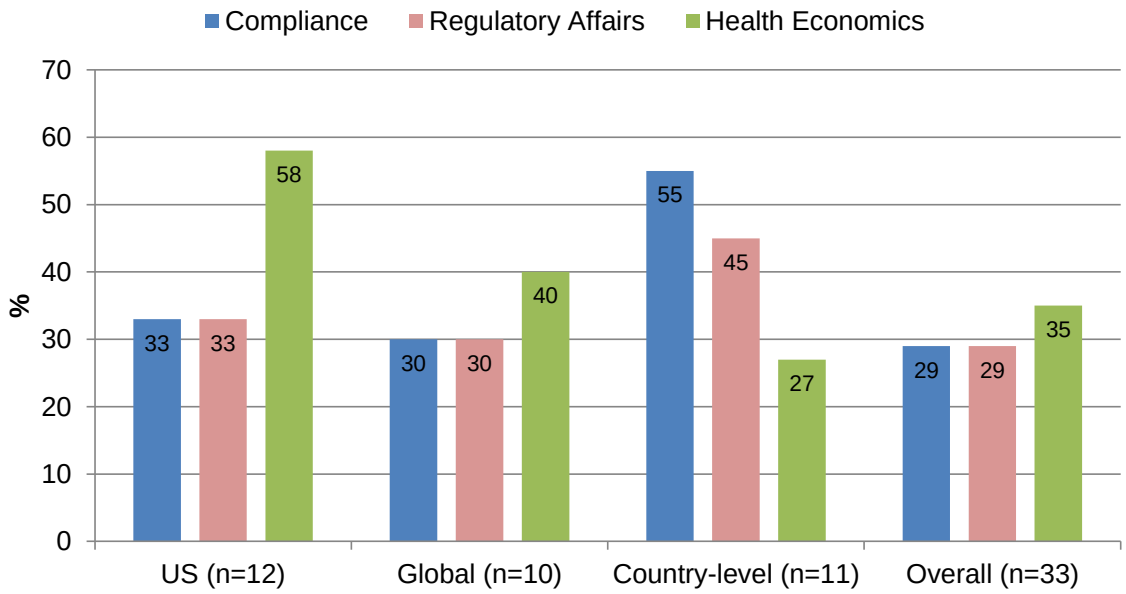

Figure 7. Proportion of medical affairs departments responsible for emerging activities, by region (adapted) (3). US, United States of America.

The health economics function, or ***pharmacoeconomics***, might be the most logical choice of these emerging potential partners to align itself with medical affairs and the bond between medical affairs and health economics is growing stronger. As seen in figure 7, surveyed pharmaceutical companies revealed that 35% of medical affairs groups take ownership over certain health economic activities. That number grows when the United States of America (US) and global medical affairs groups are broken out, where even higher percentages reported ownership of health economic activities.

The health economics team's objective is to assign euro/dollar values to patient outcomes. The health economics group must act as an impartial bridge between the clinical side of the organization and the commercial side — and is similar in that respect to medical affairs groups. Furthermore, the two departments function well together because medical affairs teams are charged with communicating the health economics information to the medical community (3).

The ***regulatory affairs*** and ***compliance*** functions also share a great deal of responsibilities with medical affairs. Overall, 29% of medical affairs groups maintain some responsibility over both regulatory affairs and compliance (Figure 7) (3).

1.3 Modern medical affairs departments structure and organization

Mainly driven by compliance issues and by the need to adapt in order to meet the needs of changing markets, many pharmaceutical companies have completely restructured their medical affairs groups over the last several years (3).

The most noteworthy change was that companies have moved their medical affairs teams out of the authorities of groups such as marketing and research and development (R&D) to create stand-alone functions focused on the different tasks and responsibilities of medical affairs (3).

This is highly perceptible in a series of consecutive surveys. In 2002, there was not one company surveyed reporting a stand-alone medical affairs group. At that time, most frequently (43%) medical affairs teams reported to marketing. In 2008, in another survey, the percentage of companies with a stand-alone medical affairs group raised to 14% and only 7% of medical affairs teams reported to marketing. The trend continued and, in 2010, 52% of the companies surveyed had stand-alone medical affairs groups (Figure 8) (3).

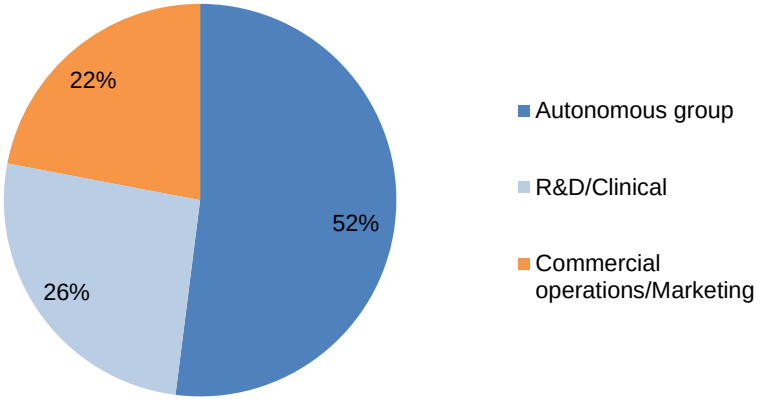

Figure 8. Function medical affairs group report to internally in 2010 (adapted) (3).

In larger companies, in addition to creating stand-alone medical affairs teams, medical affairs groups are now being centralized to streamline communication and coordination across different markets around the globe. According to a recent survey, 52% of the companies have now centralized their medical affairs teams, in global teams, in an effort to unify various medical activities across their organizations (Figure 9) (3).

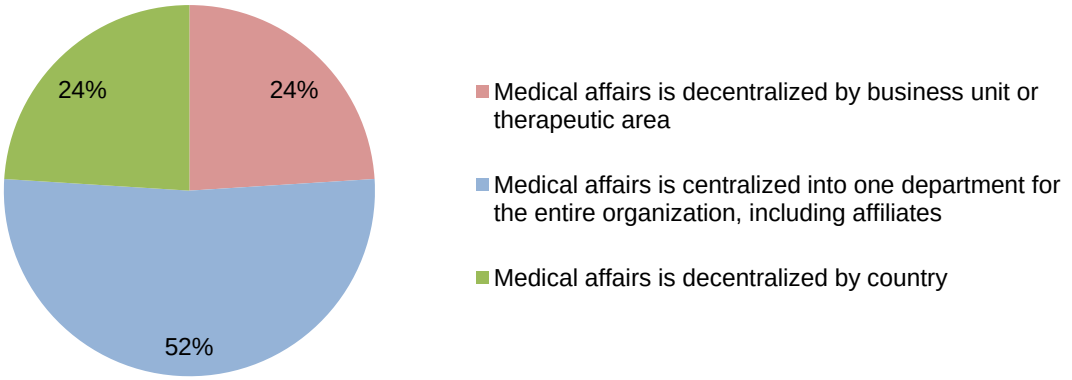

Figure 9. Medical affairs structure inside organization in 2010 (adapted) (3).

Although a global structure has its drawbacks, it creates noteworthy advantages. Arguably the greatest of these benefits is the integration of medical affairs strategies with global strategies pursued by R&D and marketing organizations.

Nevertheless, even with global teams, it is the job of regional and affiliate groups to execute medical strategies. In this instance, global medical affairs departments serve as the main communication hub for all medical affairs teams worldwide. Global groups also serve as hubs for the storage of ideas developed at different levels of the medical structure. The global team communicates those ideas to other areas that might use them to their benefit. Managing ideas and best practices at a high level helps to eliminate duplication and inefficiencies in different regions (3).

There may be as many different ways of organizing a medical affairs department as there are pharmaceutical companies and it is beyond the scope of this report to propose any specific model. Nevertheless, it should be noted that only the largest and most global medical affairs teams are composed of specific subgroups to manage each of the key activities described in section 1.2. In smaller and more local companies, there may be only a few subgroups, if any, in charge of specific tasks.

A medical affairs manager working at a national level will probably have a broader range of tasks under his responsibility and thus necessarily less time to devote and specialize in each one; another medical affairs manager working globally at a larger company will probably be dedicated and specialized in one or two of the key activities described in section 1.2.

Similarly, the range of activities that medical affairs departments are responsible for varies depending if they are working at a global or at a country level (Figures 10 and 11).

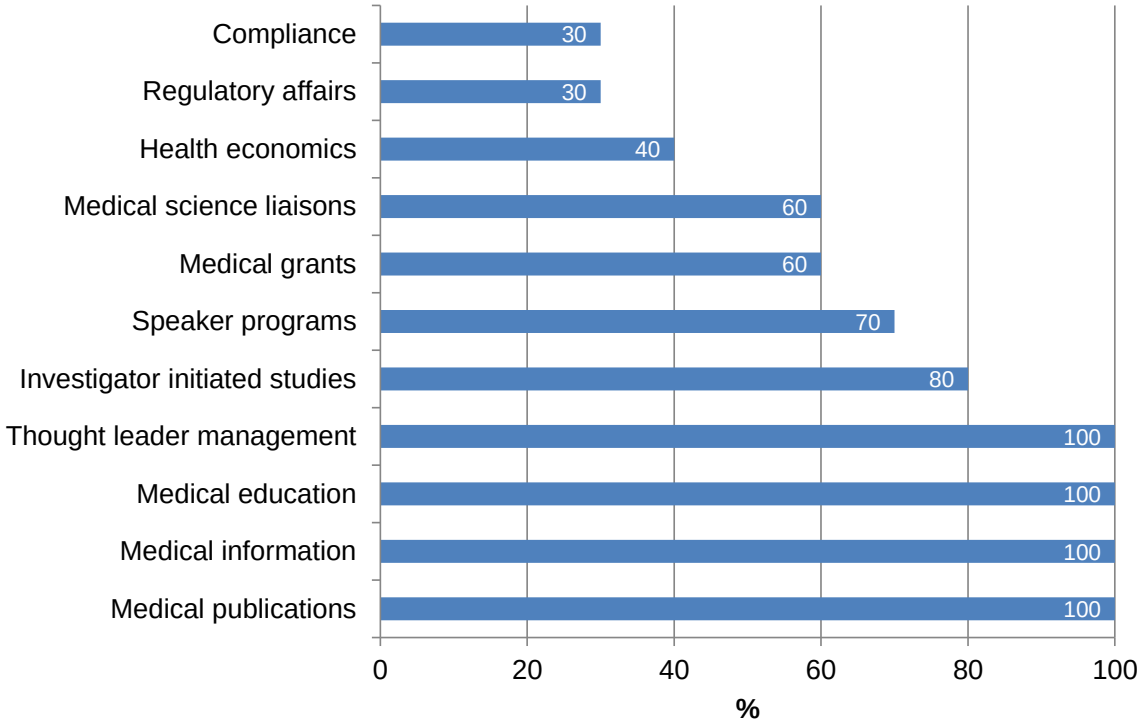

Figure 10. Proportion of global medical affairs departments responsible for activities (adapted) (3).

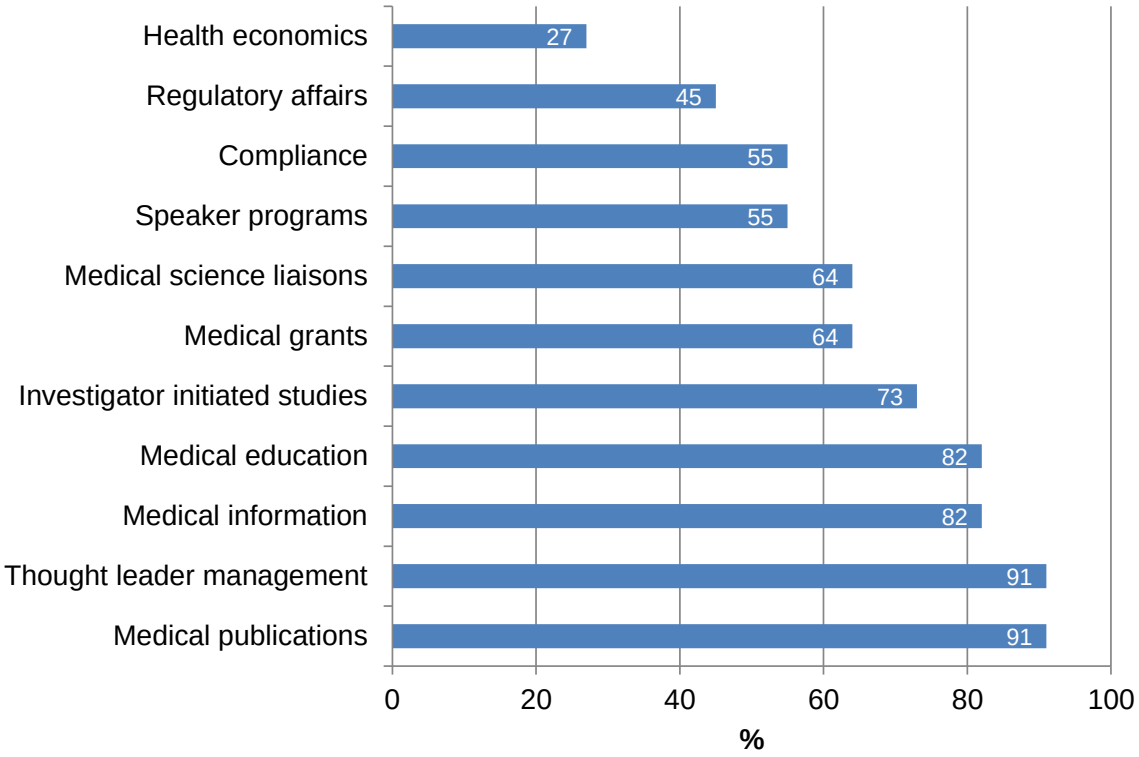

Figure 11. Proportion of country-level medical affairs departments responsible for activities (adapted) (3).

Another interesting way to analyse how important the different activities are for modern medical affairs departments is to see how they allocate funding to those activities, in terms of budget and staffing. In a recent survey to US based companies, MSL make up the largest percentage of the full time equivalents (FTEs) on medical affairs teams today (30%) and receive a significant portion of the overall budgets (16%). Thought leader development maintains its position as the second-largest staffing resource (15%) as well as budget allocation (12%) (Figure 12) (3).

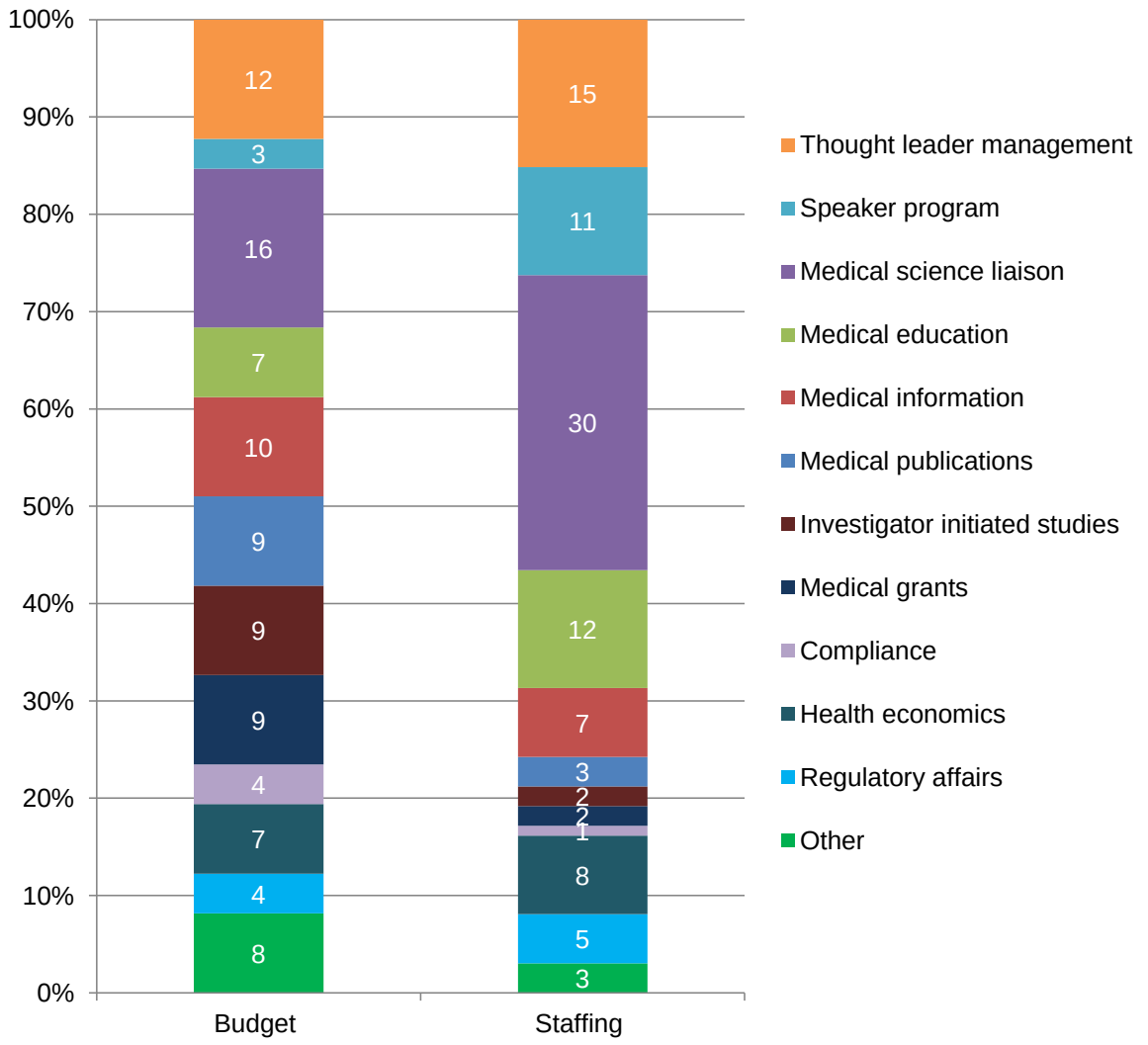

Figure 12. Medical affairs budgets and staffing resource allocation in the United States of America in 2010 (adapted) (3).

A recent report pointed out to emerging shifts in medical affairs resources that translate clear changes on the relative importance of different activities for medical affairs and companies (Figure 13) (3).

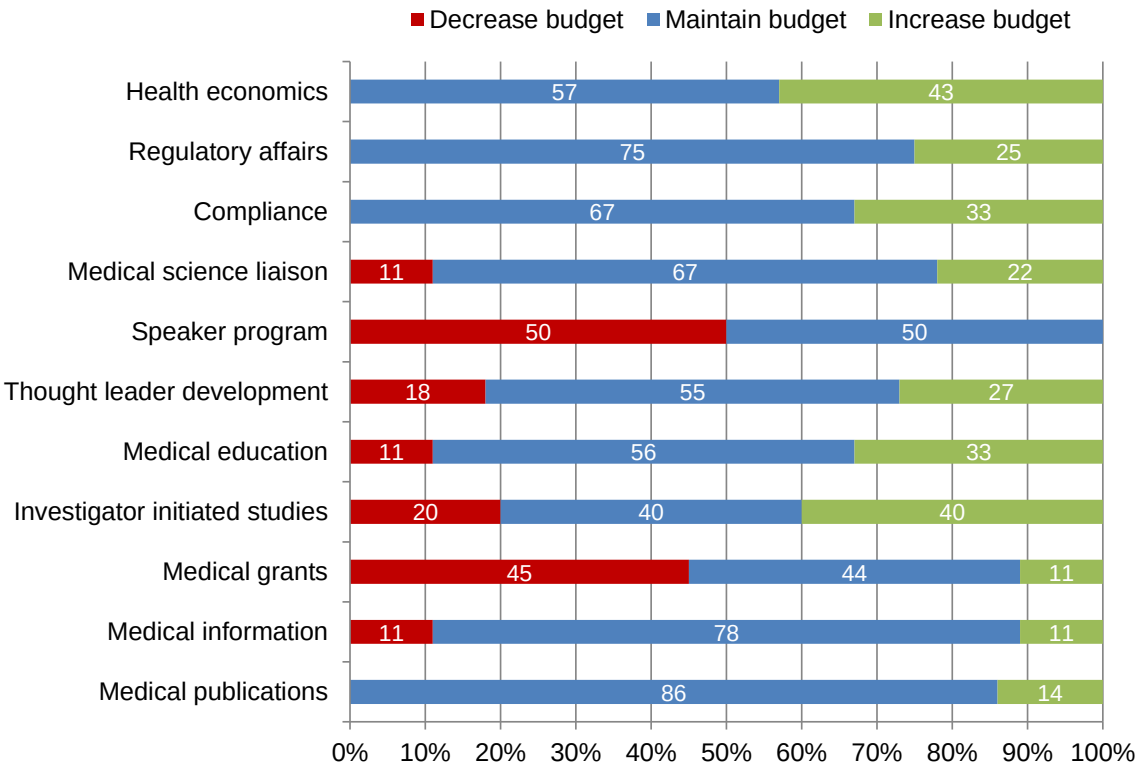

Figure 13. Shifting in budget allocation to key activities in the United States of America medical affairs departments (adapted) (3).

Noticeably, companies are moving resources away from speaker programs. Fifty percent of companies will decrease their US budgets for speaker programs. The decreasing interest in speaker programs could stem from a number of factors. As was previously mentioned, many speakers are moving away from speaking opportunities due to increased transparency regarding their roles as industry consultants; they hesitate to expose their own financial information and/or relationships with drug companies. (3).

In contrast, companies are shifting resources toward medical education, compliance, investigator-initiated trial programs and health economics activities. These latter two areas will experience notable growth: 40% of companies will increase medical affairs funding for IIS support, and 43% will increase funding for health economics. An upswing in calls for clinical data, a more competitive global marketplace, and more demanding payers are leading to increased interest in IIS and health economics.

In the different sections of this first chapter the modern affairs department and the role of the medical affairs manager in the contemporary pharmaceutical company were described with detail. Having this background information as an overall standard, the next chapter will describe my personal experience as a medical affairs manager.

2. Description of my professional experience as medical affairs manager

I have started my career as Medical Affairs Manager in November 17th 2008 at the pharmaceutical company Bial – Portela & Cª. S.A. (Bial), located in São Mamede do Coronado, Portugal, taking responsibilities over all Central Nervous System (CNS) marketed drugs in Portugal. I was also responsible for the medical management of CNS drugs marketed by Bial in some countries in Latin America, Africa and Europe (Table 1).

I have kept these responsibilities until September 1st 2011 when I became International Medical Affairs Manager at Bial, assuming the global medical management of the Bial's pipeline drugs that reach the market, being currently the case of eslicarbazepine acetate (Zebinix®). I presently still maintain this position (Table 1).

Table 1. Professional experience as medical affairs manager

Date	Position	Markets Drugs under my responsibility
17/11/2008 until 31/08/2011	CNS Medical Manager	Portugal • Paroxetine (brand name Paxetil®) • Bupropion (brand name Elontril®) • Mexazolam (brand name Sedoxil®) • Eslicarbazepine Acetate (brand names Zebinix®) Some countries in Latin America, Africa and Europe • Fixed association of ergotamine tartrate, paracetamol, caffeine and belladonna alkaloids (brand name Migrétil®) • Mexazolam (brand names Mélex® and Sedoxil) • Eslicarbazepine Acetate (brand name Zebinix®)
01/09/2011 until present	International Medical Manager	Worldwide • Eslicarbazepine Acetate (brand names Zebinix® in Europe and Stedesa™ in US and Canada)

Notes: CNS, Central Nervous System; US, United States of America

In the sections below I will describe in more detail the responsibilities and activities I have developed during these two periods, trying to use examples whenever suitable. Taking my duty of confidentially towards Bial into consideration I will only use information which is at present in the public domain and there will be consequently some cases where details of activities cannot be provided.

2.1. Professional Experience as a CNS Medical Affairs Manager

As the medical affairs manager responsible for all CNS drugs marketed by Bial in Portugal and also in some countries in Latin America, Africa and Europe I have developed a comprehensive set of different tasks:

- I have assisted the organization of several scientific meetings by inviting national and international speakers and by revising and approving the contents of the lectures, ensuring both their scientific accuracy and their compliance with ethical and deontological applicable regulations. Amongst the several meetings which had my scientific coordination I would like to highlight the following ones:
    - Bial Neurology Forum 2009
    - Bial Neurology Forum 2010
    - Bial Psychiatry Forum 2010
    - Bial Neurology Forum 2011
    - Bial Neurology Forum 2012

  More details regarding the scientific programmes of these events mentioned above may be found in Annex 1.

- I have been responsible for the continuous training of sales representatives and other staff from marketing and sales departments, ensuring they had the necessary knowledge to execute their professional activity in the strict compliance with ethical and deontological norms. I have completed more than 100 hours of training covering different scientific areas from basic anatomy and physiology to disease management and therapeutics.

- I have helped in the preparation and I revised and approved more than 120 promotional materials ensuring they were compliant with ethical and deontological regulations namely confirming the delivered information was accurate, balanced, fair, objective and sufficiently complete to enable the recipient to form his own opinion of the therapeutic value of the medicinal product concerned.

- I have addressed more than 130 unsolicited medical questions ensuring a timely reply to all of them and triaging all questions that could potentially be related with adverse events or other safety issues related to use of a medicinal product.

- I have been a keynote speaker or chairman in more than 20 scientific meetings where the best available evidence related with the drugs under my responsibility was presented.
- I have prepared more than 10 expert opinion reports related to the therapeutic value of CNS drugs that could be potentially licensed to Bial.
- I have closely cooperated with Bial's regulatory department by supporting the preparation of more than 10 registry dossiers and other expert opinion reports.
- I have actively participated in the design and implementation of one phase IV study in Portugal that is currently ongoing.
- I have supported the implementation of two investigator initiated studies.
- I have worked in close cooperation with Bial's pharmacovigilance department assuming an especially active role in:
    - addressing all unsolicited medical questions that were identified as being related with safety issues associated with the use of a medicinal product;
    - following-up notifications of adverse events related with the use of a medicinal product;
    - creating a tracking-log that supports the monitoring of replies to unsolicited medical questions;
    - preparing a monthly report of unsolicited medical questions as a basis for the reconciliation of safety information;
    - assisting in the preparation of Periodic Safety Update Reports.

2.2. Professional Experience as International Medical Manager

Being responsible for the global medical management of eslicarbazepine acetate (brand names Zebinix® in Europe and Stedesa™ in US and Canada) I have developed the following key activities:

- I have established and managed the eslicarbazepine acetate scientific communication plan, including:
    - Draft and revision of original manuscripts;
    - Preparation of all activities related to scientific communication at major international congresses, namely draft, revision and submission of abstracts, creation and revision of posters and preparation and revision of oral communications;
    - Creation and revision of a standardized slide deck containing the most updated available evidence regarding eslicarbazepine acetate, to be used as a key source of information for different stakeholders, such as Bial marketing and regulatory departments, physicians and external partners.

  All these activities were done in close cooperation with several internal and external stakeholders such as Bial's clinical and non-clinical research teams, and regulatory and legal departments, external authors and external partners.

  Some of the above mentioned manuscripts have already been published and the list of references as well as the corresponding abstracts may be found in Annex 2. As an example, the posters recently presented at the 10th European Congress on Epileptology, held in London, from September 30th till October 4th 2012, are available in Annex 3.

  - I have implemented post-hoc analysis using the available database from phase III pivotal trials. Three of these post-hoc analyses were accepted as poster presentation at the forthcoming 66th American Epilepsy Society meeting, to be held in San Diego from November 30th till December 4th 2012 (abstracts are already available online at http://www.aesnet.org/go/publications/aes-abstracts/abstract-search and may be found in Annex 4).

- I have designed and implemented phase IIIb/IV studies, actively participating in:

  - writing of the protocol, the case report form and other study related documents;
  - selection of Contract Research Organizations;
  - selection and invitation of research centres;
  - training of research centres.

- I have written and continuously updated 3 training manuals for the scientific preparation of different stakeholders, such as sales representatives and other staff from marketing and sales departments, regarding the topics of Epilepsy Management and Eslicarbazepine Acetate.
- I have written, revised or continuously updated more than 10 standardized response letters to unsolicited medical questions related to eslicarbazepine acetate.
- I have created and maintained a database of all published information related with eslicarbazepine acetate.
- I have liaised with external partners to whom Bial yielded eslicarbazepine acetate commercialization or development rights in Europe and in the US, managing all medical affairs issues, namely publications and other public disclosure of data, promotional activities, market access, strategic marketing and positioning, *etc.*
- I have assisted Bial's regulatory department in several activities related with eslicarbazepine acetate.
- I have closely cooperated with Bial's pharmacovigilance department in all issues related to eslicarbazepine acetate, namely unsolicited medical questions, follow-up of report of adverse events and helped in the preparation of Periodic Safety Update Reports and Development Safety Update Reports.

3. Critical appraisal of my professional experience

During my experience of almost 4 years as a medical affairs manager, I had the chance to progressively undertake more responsibilities, initially working at a more operational and local level and subsequently assuming a more strategic role in a global position.

In this route I have performed a wide variety of tasks that covered all the range of activities performed by medical affairs managers.

I have started my career as a CNS Medical Affairs Manager providing a more direct support to marketing, regulatory and pharmacovigilance activities related to Bial's CNS marketed drugs in Portugal and also in some Latin American, African and European countries. When I became International Medical Affairs Manager I also took responsibilities related to phase IV clinical development, scientific communication management and medical writing, post-hoc analysis and global marketing support.

Being a physician specialized in Public Health, with a particular interest and expertise in Epidemiology, I have inherently carried most of my key values and competencies to the role in a pharmaceutical company which I believe positively impacted my performance.

As a Public Health physician, my ultimate goal is to contribute meaningfully for a sustained population-wide health improvement (6), which I always tried to do while playing my role as a medical affairs manager. In other words, I never stopped being a Public Health physician.

As an Epidemiologist, I had the necessary skills to analyse and interpret available data, transforming it in useful information that could be used by both Bial's departments (marketing, regulatory, pharmacovigilance, *etc.*) as well as external stakeholders, such as prescribing physicians, patients, regulatory authorities and Bial's partners. Furthermore, I was able to identify information gaps, providing guidance on how to fill them, either through the proposal, design and implementation of phase IIIb/IV studies, conducting post-hoc analysis or advising on phase I to III further clinical development.

I have always aimed at excellence while performing the activities under my responsibility, pursuing innovation as one key element to achieve that goal, which has been recognized by my peers and superiors, when I was granted the "Medical Affairs Department Award 2011" (Annex 5).

I have also been able to establish fruitful relationships with all external stakeholders, such as physicians, patients, Bial's partners and official entities, acting as a reliable source of information and advice.

In conclusion, I believe I have successfully played my role as a medical affairs manager, as I have positively contributed to the success of my company, through an excellent performance of the tasks under my responsibility while attaining the highest professional and ethics standards.

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6. Beaglehole R, Bonita R, Horton R, Adams O, McKee M. Public health in the new era: improving health through collective action. Lancet2004 Jun 19;363(9426):2084-6.

ANNEXES

Annex 1 – Scientific Program of key meetings which had my scientific coordination

Fórum Bial de Neurologia 2009

21 de Novembro Lisboa, Pestana Palace Hotel

mediBial

Fórum Bial de Neurologia 2009

programa científico

14h30 Abertura do secretariado

15h00 Demência na ordem do dia

Demência com Corpos de Lewy – perspectiva clínica

João Massano, Médico Interno de Neurologia, Hospital de São João, assistente da Faculdade de Medicina da Universidade do Porto

Apresentação e comentário: **Carolina Garrett**, Directora do Serviço de Neurologia, Hospital de São João, Professora Associada de Neurologia da Faculdade de Medicina da Universidade do Porto

Biomarcadores laboratoriais no diagnóstico precoce da demência

Inês Baldeiras, Investigadora da Faculdade de Medicina da Universidade de Coimbra, Laboratório de Neuroquímica dos Hospitais da Universidade de Coimbra

Apresentação e comentário: **Isabel Santana**, Neurologista, Hospitais da Universidade de Coimbra, Professora Auxiliar de Neurologia da Faculdade de Medicina da Universidade de Coimbra

As alterações da substância branca cerebral: o que sabemos depois do estudo LADIS

Ana Verdelho, Neurologista do Departamento de Neurociências do Hospital de Santa Maria, Investigadora do Instituto de Medicina Molecular

Apresentação e comentário: **Alexandre de Mendonça**, Neurologista e Investigador Principal, Faculdade de Medicina da Universidade de Lisboa, Instituto de Medicina Molecular

16h30 Coffee-Break

17h00 Acetato de eslicarbazepina – do laboratório à prática clínica

Moderadores:

José Lopes-Lima, Presidente da Liga Portuguesa Contra a Epilepsia
Francisco Pinto, Presidente cessante da Liga Portuguesa Contra a Epilepsia

Da descoberta de uma nova molécula aos ensaios clínicos

Patrício Soares da Silva, Director do Departamento de Investigação e Desenvolvimento BIAL

From Clinical Trials to Clinical Practice

Antonio Gil-Nagel, Serviço de Neurologia (Programa de Epilepsia), Hospital Ruber Internacional, Madrid, Espanha

Beyond seizure control – why is it important to evaluate quality of life and depressive symptoms in epilepsy patients?

Joyce Cramer, *President of Epilepsy Therapy Project, Associate Research Scientist, Yale University School of Medicine, USA*

Jantar de encerramento

Fórum Bial de Neurologia

2010

20 de Novembro

Grande Real Villa Itália
Hotel & SPA • Cascais

10.30h /////// Abertura do Secretariado

WORKSHOP EPILEPSIA

11.30h – 13.00h
Depression and Epilepsy: Neurobiological perspectives and seizure therapeutical implications
Palestrante: Andrés Kanner
Moderadores: Henrique Pereira / José Manuel Lopes Lima

13.00h – 14.15h /////// Almoço Buffet

14.15h – 15.00h
Depression and Epilepsy: Neurobiological perspectives and seizure therapeutical implications
Sessão Interactiva de Casos Clínicos – Rute Teotónio e Catarina Cunha
Moderadores: Henrique Pereira / José Manuel Lopes Lima / Andrés Kanner

15.00h – 16.00h
MRI negative. What else?
Palestrante: Mathias Koepp
Moderadores: Egídio Machado / José Pimentel

16.00h – 16.30h /////// *Coffee-Break*

16.30h – 17.15h
MRI negative. What else?
Sessão Interactiva de Casos Clínicos – Ana Patrícia Antunes e Francisca Sá
Moderadores: Egídio Machado / José Pimentel / Mathias Koepp

17.15h – 18.15h
Epileptic networks on EEG/fMRI
Palestrante: Louis Lemieux
Moderadores: Francisco Sales / Miguel Castelo-Branco

18.15h – 18h30 /////// *Coffee-Break*

18.30h – 19.15h
Epileptic networks on EEG/fMRI
Sessão Interactiva de Casos Clínicos – Alberto Leal e Gil Cunha
Moderadores: Francisco Sales / Miguel Castelo-Branco / Louis Lemieux

WORKSHOP DEMÊNCIA

11.30h – 13.00h
Clinical diagnosis of Alzheimer's disease
Palestrante: John C. Morris

14.15h – 16.00h
Clinical diagnosis of Alzheimer's disease
Clinical Dementia Rating practical training using videotaped assessments
Palestrante: John C. Morris

16.30h – 17.30h
Current therapy of Alzheimer's disease and drug classes under investigation for "disease-modifying" therapy
Palestrante: John C. Morris

17.30h – 18.30h
Research advances in Alzheimer's disease
Palestrante: John C. Morris

Desenvolvido em parceria com o

lpce

20.00h ////// Jantar

FÓRUM BIAL DE PSIQUIATRIA 2010

19 JUNHO
VILA GALÉ COIMBRA

Patrocínio Científico de:

Sociedade Portuguesa de Psiquiatria e Saúde Mental

PROGRAMA CIENTÍFICO

>>> 8h – Pequeno-almoço "Conheça os mestres"

>>> 9h30 – Sessão de Abertura

Prevenção do suicídio
Jan Fawcett, Faculdade de Medicina da Universidade do Novo México
Moderador: Nazaré Santos, Presidente da Sociedade Portuguesa de Suicidologia

>>> 10h45 – Coffee-break

>>> 11h15 – 1ª Sessão

O papel actual da neuroimagem na psiquiatria
– prática clínica e investigação
Nancy Andreasen, Faculdade de Medicina da Universidade de Iowa
Moderador: Maria Luísa Figueira, Hospital de Santa Maria, Lisboa

>>> 12h30 – Actualização breve

Acetato de Eslicarbazepina
– dos ensaios clínicos ao desafio do tratamento da epilepsia
Henrique Pereira, Hospital Magalhães de Lemos, Porto
Moderador: Rui Sousa, Secção de Assuntos Médicos BIAL

>>> 13h – Almoço

>>> 14h30 – 2ª Sessão

Era uma vez... (A história da depressão)

- **Será que temos melhores ou piores classificações?**
  Julio Vallejo Ruiloba, Faculdade de Medicina da Universidade de Barcelona
- **Temos muitos mais antidepressivos mas estamos realmente a tratar melhor os nossos doentes?**
  Manuel Esteves, Hospital de São João, Porto
- **Estará a sexualidade a tornar-se mais importante no tratamento da depressão?**
  Francisco Allen Gomes, Sociedade Portuguesa de Sexologia Clínica

Moderador: António Roma Torres, Hospital de São João, Porto

>>> 16h15 – Controvérsias

Benzodiazepinas: Deus ou Diabo?
Manuel Guerreiro, Director Clínico da Casa de Saúde de Carnaxide
No limbo do tratamento com fármacos antidemenciais...
Horácio Firmino, Hospitais da Universidade de Coimbra
Moderador: Manuel Esteves, Hospital de São João, Porto

>>> 17h15 – Coffee-Break

>>> 17h45 – 3ª Sessão

DSM-5: será que estará à altura das expectativas?
Jan Fawcett, Membro do Grupo de trabalho de elaboração do DSM-5
Moderador: Julio Vallejo Ruiloba, Faculdade de Medicina da Universidade de Barcelona

>>> 19h – Encerramento

António Pacheco Palha, Presidente da Sociedade Portuguesa de Psiquiatria e Saúde Mental.

>>> 20h – Jantar

Bial

O importante é não pararmos de nos interrogarmos.

The important thing is not to stop questioning.

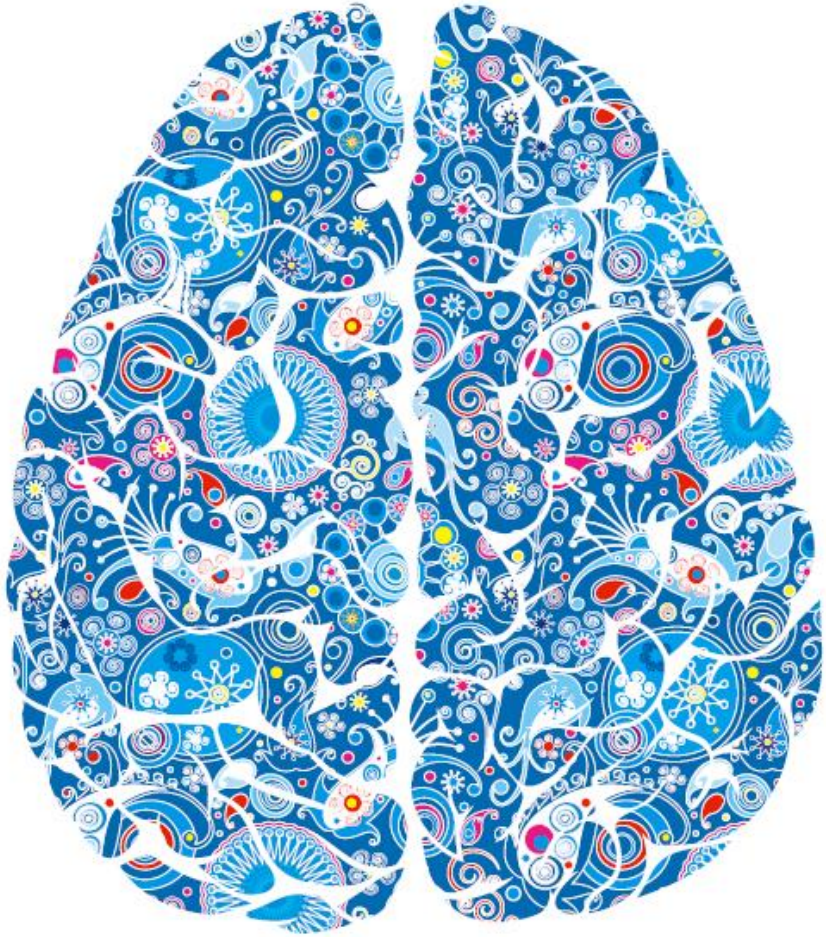
Albert Einstein

Bial

4º Fórum Bial de Neurologia 2011

19 de Novembro, Lisboa

Tivoli Palacete/Centro de Reuniões e Eventos



Workshop Epilepsia

11.00 – Abertura do Secretariado

11.30 - 13.00
Mesa 1 – Epilepsy: new etiologies
Moderadores: J. Pimentel / Pedro Cabral

11.30 - 12.15
Epilepsy and channelopathies
Palestrante: Pierre Genton

12.15 - 13.00
Epilepsy and immuno-mediated encephalitis
Palestrante: Joseph Dalmau

13.00 – 14.15 – Almoço

14.15 - 15.00 – Clinical cases
Clinical cases will be presented in 10 minutes with 5 minutes for individualised discussion.
Moderadores: J. Pimentel / Pedro Cabral / Pierre Genton / Joseph Dalmau

14.15 - 14.30
Case 1 – Ana Massano, Serviço de Neurologia, Hospitais da Universidade de Coimbra

14.30 - 14.45
Case 2 – Vânia Almeida, Serviço de Neurologia, Hospital de Santa Maria (CHLN, EPE), Lisboa

14.45 - 15.00
Case 3 – Rui Loureiro / Fernando Correia, Centro Hospitalar do Porto

15.00 - 16.30
Mesa 2 – Epilepsy / Cognition / Behaviour
Moderadores: Lopes Lima / Isabel Santana

15.00 - 15.45
Neuropsychological assessment of epilepsy in infancy
Palestrante: Ana Filipa Lopes

15.45 - 16.30
Epilepsy / Cognition / Behaviour
Palestrante: Anne T. Berg

16.30 – 17.00 – Coffee break

17.00 - 17.45 – Clinical cases
Clinical cases will be presented in 10 minutes with 5 minutes for individualised discussion.
Moderadores: Lopes Lima / Isabel Santana / Ana Filipa Lopes/ Anne T. Berg

17.00 - 17.15
Case 1 – Margarida Henriques, Centro Hospitalar de Coimbra, Hospital Pediátrico

17.15 - 17.30
Case 2 – Cláudia Guarda, Serviço de Neurologia, Hospital Garcia de Orta, Almada

17.30 - 17.45
Case 3 – Manuela Santos, Hospital Maria Pia, Centro Hospitalar do Porto

Desenvolvido em parceria com a Ipce

Workshop Demência

11.00 – Abertura do Secretariado

11.45 - 13.00
Management of behavioural changes in dementia – tips and tricks
Palestrante: Clive Ballard

13.00 – 14.15 – Almoço

14.30 - 16.00
Can we prevent dementia?
Palestrante: Clive Ballard and Anne Corbett

16.30 – 17.00 – Coffee break

16.30 - 18.00
Dementia with Lewy Bodies and Parkinson's disease dementia
Palestrante: Clive Ballard

18.00
Q&A and Final Remarks

Ciência & Arte

5º FORUM Bial de Neurologia

20 de outubro 2012

Fundação de Serralves, Porto

Desenvolvido em parceria com a

Ipce

LIGA PORTUGUESA CONTRA A EPILEPSIA

AGENDA

11:30 **Opening of the Secretariat**

12:00 **Key note BIAL**

António Portela [CEO Bial]

12:05 **Key note LPCE**

Ricardo Rego [Portuguese League Against Epilepsy]

12:15 / 13:30 **Platform 1 – Reproductive Aspects of Epilepsy**

Chairman: José Pimentel and **Torbjörn Tomson**

12:15 / 13:00 **Lecture – An update of women and men issues**

Speaker: Torbjörn Tomson [Department of Neurology, Karolinska University Hospital, Stockholm, Sweden]

13:00 / 13:30 **Clinical Cases Discussion**

13:00 / 13:15 **Case 1**

Paulo Coelho [Department of Neurology, Centro Hospitalar e Universitário de Coimbra, Portugal]

13:15 / 13:30 **Case 2**

Rute Teotónio [Department of Neurology, Centro Hospitalar e Universitário de Coimbra, Portugal]

13:30 / 15:00 **Lunch**

15:00 / 16:30 **Platform 2 – Epilepsy and Sleep**

Chairman: Lopes Lima and **Jan Rémi**

15:00 / 15:45 **Lecture – Emerging views on epilepsy and sleep**

Speaker: Jan Rémi [Epilepsy Center & Neurological Sleep Center, Dept. of Neurology, Ludwig-Maximilians-Universität, Munich, Germany]

15:45 / 16:30 **Clinical Cases Discussion**

15:45 / 16:00 **Case 1**

Isabel Moreira [Department of Neurology, Hospital de Santo António, Centro Hospitalar do Porto, Portugal]

16:00 / 16:15 **Case 2**

Tiago Teodoro [Department of Neurology, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Portugal]

16:15 / 16:30 **Case 3**

Inês Marques [Department of Neurology, Centro Hospitalar e Universitário de Coimbra, Portugal]

16:30 **Closing remarks**

16:35 / 17:00 **Coffee-break**

17:00 / 18:30 **BIAL Symposium**

Chairman: Patrício Soares-da-Silva [Director of Department of Research and Development, BIAL – Portela & Cª, S.A., S. Mamede do Coronado, Portugal and Director of Department of Pharmacology and Therapeutics, Faculty of Medicine, Universidade do Porto, Portugal]

17:00 / 17:30 **Lecture – Eslicarbazepine acetate update: from a unique pharmacological profile to a distinctive clinical experience**

Speaker: Christian Elger [Department of Epileptology, University of Bonn, Bonn, Germany]

17:30 / 18:00 **Clinical experience 1 – One year clinical experience with eslicarbazepine acetate on a community hospital in Porto, Portugal**

Speaker: João Chaves [Department of Central Nervous System and Senses Organs, Hospital Santo António, Porto, Portugal]

18:00 / 18:30 **Clinical experience 2 – Prospective Post-Authorization Observational Study of Eslicarbazepine Acetate in the Treatment of Pharmacoresistant Epilepsies**

Speaker: Rodrigo Rocamora [Director of the Epilepsy Unit, Department of Neurology, Hospital del Mar, Barcelona, Spain]

18:30 **Closing remarks**

Annex 2 – References and abstracts of published full-papers in which I actively participated in the review process

1. **Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. Epilepsia Jun;53(6):935-46.**

SUMMARY

Eslicarbazepine acetate (ESL) is a novel once-daily antiepileptic drug (AED) approved in Europe since 2009 that was found to be efficacious and well tolerated in a phase III clinical program in adult patients with partial onset seizures previously not controlled with treatment with one to three AEDs, including carbamazepine (CBZ). ESL shares with CBZ and oxcarbazepine (OXC) the dibenzazepine nucleus bearing the 5-carboxamide substitute, but is structurally different at the 10,11 position. This molecular variation results in differences in metabolism, preventing the formation of toxic epoxide metabolites such as carbamazepine-10,11-epoxide. Unlike OXC, which is metabolized to both eslicarbazepine and (R)-licarbazepine, ESL is extensively converted to eslicarbazepine. The systemic exposure to eslicarbazepine after ESL oral administration is approximately 94% of the parent dose, with minimal exposure to (R)-licarbazepine and OXC. After ESL oral administration, the effective half-life (t1/2,eff) of eslicarbazepine was 20–24 h, which is approximately two times longer than its terminal half-life (t1/2). At clinically relevant doses (400–1,600 mg/day) ESL has linear pharmacokinetics (PK) with no effects of gender or moderate liver impairment. However, because eslicarbazepine is eliminated primarily (66%) by renal excretion, dose adjustment is recommended for patients with renal impairment. Eslicarbazepine clearance is induced by phenobarbital, phenytoin, and CBZ and it dose-dependently decreases plasma exposure of oral contraceptive and simvastatin.

KEY WORDS: Antiepileptic drugs, Eslicarbazepine acetate, Eslicarbazepine, Pharmacokinetics, Drug interactions.

2. **Gil-Nagel A, Elger C, Ben-Menachem E, Halasz P, Lopes-Lima J, Gabbai AA, et al. Efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: Integrated analysis of pooled data from double-blind phase III clinical studies. Epilepsia Aug 6.**

SUMMARY

Purpose: To evaluate the efficacy and safety profile of eslicarbazepine acetate (ESL) added to stable antiepileptic therapy in adults with partial-onset seizures.

Methods: Data from 1,049 patients enrolled from 125 centers, in 23 countries, in three phase III double-blind, randomized, placebo-controlled studies were pooled and analyzed. Following a 2-week titration period, ESL was administered at 400 mg, 800 mg, and 1,200 mg once-daily doses for 12 weeks.

Key Findings: Seizure frequency was significantly reduced with ESL 800 mg ($p < 0.0001$) and 1,200 mg ($p < 0.0001$) compared to placebo. Median relative reduction in seizure frequency was, respectively, 35% and 39% (placebo 15%) and responder rate was 36% and 44% (placebo 22%). ESL was more efficacious than placebo regardless of gender, geographic region, epilepsy duration, age at time of diagnosis, seizure type, and number and type of concomitant antiepileptic drugs (AEDs). Incidence of adverse events (AEs) and AEs leading to discontinuation were dose dependent. AEs occurred mainly during the first weeks of treatment, with no difference between groups after 6 weeks. Most common AEs (>10% patients) were dizziness, somnolence, and headache. The incidence of AEs in ESL groups compared to placebo was generally consistent among different subpopulations.

Significance: Once-daily ESL 800 mg and 1,200 mg showed consistent results across all efficacy and safety end points. Results were independent of study population characteristics and type and number of concomitant AEDs.

KEY WORDS: Adjunctive therapy, Adults, Antiepileptic drugs, Eslicarbazepine acetate, Partial-onset seizures, Refractory epilepsy.

3. **Hufnagel A, Ben-Menachem E, Gabbai AA, Falcao A, Almeida L, Soares-da-Silva P. Long-term safety and efficacy of eslicarbazepine acetate as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy: Results of a 1-year open-label extension study. Epilepsy Res Aug 4.**

SUMMARY

Objective: To evaluate the long-term safety, tolerability and efficacy of once-daily eslicarbazepine acetate (ESL) as adjunctive therapy in adults with partial-onset seizures.

Methods: One-year open-label extension (OLE) study with ESL in patients who completed a randomised, double-blind placebo-controlled trial (study BIA-2093-302; Epilepsy Res. 89 (2010) 278—285). Starting dose was 800 mg once-daily, for 4 weeks; thereafter, dose could be individualised within the 400—1200 mg range. Doses of concomitant antiepileptic drugs were to be kept stable.

Results: Overall, 325 patients were enrolled (intent-to-treat population); 223 (68.6%) patients completed 1-year of treatment. ESL median dose was 800 mg once-daily. Compared to the base-line period of the double-blind study completed prior to this OLE study, median seizure frequency decreased by 32% in weeks 1—4, and between 37% and 39% thereafter. The responder rate (seizure reduction $\geq$ 50%) was 37% during weeks 1—4 and thereafter ranged between 38% and 42% per 12-week interval. Proportion of seizure-free patients per 12-week interval ranged between 5% and 11%. Improvements from baseline in several Quality of Life in Epilepsy Inventory-31 (QOLIE-31) and Montgomery Asberg Depression Rating Scale (MADRS) scores were observed. Adverse events (AEs) were reported by 83% of patients. AEs occurring in $\geq$ 10% of patients were dizziness, headache and somnolence. AEs were usually of mild to moderate intensity.

Conclusion: In this study, ESL demonstrated a sustained therapeutic effect and was well tolerated during 1-year add-on treatment of adults with partial-onset seizures. Additionally, significant improvements in quality of life domains and depressive symptoms were observed under long-term treatment with once-daily ESL.

4. **Mauri-Llerda JA. [Eslicarbazepine acetate: a novel therapeutic alternative in the treatment of focal seizures]. Rev Neurol May 1;54(9):551-5.**

RESUMEN.

La epilepsia es una de las enfermedades neurológicas más frecuentes. En los últimos años se ha incorporado a nuestras opciones terapéuticas un número muy importante de fármacos. Desde la introducción de los primeros fármacos antiepilépticos, conocidos como clásicos o convencionales, los recientemente introducidos en el mercado poseen mecanismos de acción diferentes o estructuras químicas modificadas con el objeto de proporcionar una efectividad clínica optimizada. El acetato de eslicarbacepina pertenece a este último grupo, siendo un novedoso inhibidor de los canales de sodio activados por voltaje de una sola toma diaria, con actuación selectiva en los grupos de neuronas de activación rápida. Ha sido aprobado como indicación en terapia asociada en adultos con crisis de inicio parcial, con o sin generalización secundaria. Se metaboliza ampliamente a eslicarbacepina y, en menor proporción, a R-licarbacepina y oxcarbacepina. En dosis de 800 y de 1.200 mg, ha demostrado una reducción significativa en un porcentaje elevado de pacientes con epilepsia farmacorresistente en tratamiento de forma simultánea con hasta tres fármacos antiepilépticos, y esta eficacia se mantiene en los estudios abiertos de seguimiento hasta de un año de duración. Su tolerabilidad es, por lo general, buena; la mayor parte de efectos adversos son de intensidad leve a moderada, siendo bajo el porcentaje de pacientes que retiran el tratamiento por este motivo. El acetato de eslicarbacepina constituye una alternativa de tratamiento en terapia asociada en los pacientes con epilepsia parcial que no responden de forma adecuada al tratamiento en monoterapia.

Palabras clave. Acetato de eslicarbacepina. Epilepsia. Epilepsia refractaria. Eslicarbacepina. Fármacos antiepilépticos. Oxcarbacepina. S-licarbacepina.

5. **Nunes T, Rocha JF, Falcao A, Almeida L, Soares-da-Silva P. Steady-state plasma and cerebrospinal fluid pharmacokinetics and tolerability of eslicarbazepine acetate and oxcarbazepine in healthy volunteers. Epilepsia Jul 19.**

SUMMARY

Purpose: To evaluate the pharmacokinetics and tolerability of once-daily eslicarbazepine acetate (ESL) and twice-daily oxcarbazepine (OXC) and their metabolites in cerebrospinal fluid (CSF) and plasma following repeated oral administration.

Methods: Single-center, open-label, randomized, parallel-group study in healthy volunteers. Volunteers in ESL group (n = 7) received 600 mg on days 1–3 and 1,200 mg on days 4–9, once daily. Volunteers in the OXC group (n = 7) received 300 mg on days 1–3 and 600 mg on days 4–9, twice daily. Plasma and CSF sampling was performed following the last dose.

Key Findings: Eslicarbazepine was the major drug entity in plasma and CSF, accounting for, respectively, 93.84% and 91.96% of total exposure in the ESL group and 78.06% and 76.42% in the OXC group. The extent of exposure to drug entities R-licarbazepine and oxcarbazepine was approximately four-fold higher with OXC as compared with ESL. There was relatively little fluctuation from peak-to-trough (ratio) in the CSF for both eslicarbazepine (ESL = 1.5; OXC = 1.2) and R-licarbazepine (ESL = 1.2; OXC = 1.2). In contrast, oxcarbazepine showed larger differences between peak and trough (ESL = 3.1; OXC = 6.4). A total of 84 and 24 treatment-emergent adverse events (TEAEs) were reported with OXC and ESL, respectively.

Significance: In comparison to OXC, administration of ESL resulted in more eslicarbazepine, less R-licarbazepine, and less oxcarbazepine in plasma and CSF, which may correlate with the tolerability profile reported with ESL. The smaller peak-to-trough fluctuation of eslicarbazepine in CSF (a measure of sustained delivery to the brain) than in plasma supports once-daily dosing of ESL.

KEY WORDS: Eslicarbazepine acetate, Oxcarbazepine, Pharmacokinetics, Cerebrospinal fluid, Tolerability, Healthy volunteers.

Annex 3 – Posters presented at the 10th European Congress on Epileptology, London, September 30th – October 4th 2012

Eslicarbazepine does not alter proliferation and cell cycle distribution of neural stem cells isolated from the rat subventricular zone

Morte MI[1], Carreira BP[1], Soares-da-Silva P[2,3], Araújo IM[4], Carvalho CM[1]

[1]University of Coimbra, Coimbra, Portugal; [2]BIAL - Portela & Ca. SA, S. Mamede do Coronado, Portugal; [3]University of Porto, Porto, Portugal; [4]University of Algarve, Faro, Portugal

PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1).

It has been described that antiepileptic drugs (AEDs) may alter proliferation and neurogenesis in *in vitro* and in *in vivo* models. Valproic acid (VPA) was showed to induce neuronal differentiation in hippocampal neural progenitor cells cultures (2), and inhibited proliferation of neural stem cells from the subventricular zone of adult mice (3). Moreover, it was observed that lamotrigine (LTG) and VPA increased the ratio of astrocytes versus neurons, while carbamazepine (CBZ) had the opposite effect (4). Actually, VPA, CBZ, and LTG have histone deacetylase inhibitor properties which may be associated with anti-proliferative effects (5, 6).

The aim of this study is to investigate the effect of ESL and its metabolites eslicarbazepine and R-licarbazepine, CBZ, oxcarbazepine (OXC), LTG and VPA on the proliferation of cultured neural stem cells isolated from the rat subventricular zone.

METHODS

Neural stem cells cultures were prepared from the SVZ of Wistar rats (P7-8), and were cultured as neurospheres, in medium containing EGF and EGF-2 during 8-10 days.

Cultures were passaged twice a week until the 4th passage. They were plated and kept for 2-3 days until confluency.

Cultured cells were exposed to AEDs for 24h. 5-ethynyl-2'-deoxyuridine (EdU) (10 µM) was added 4h before the cells were harvested, fixed and permeabilized with 70% EtOH overnight (4ºC).

Cells were labeled with Alexa Fluor® 488 azide for 30 min. Ribonuclease A and 7-AAD were added to the cells and the samples were analyzed on a standard BD FACSCalibur flow cytometer (BD Biosciences).

Cell cycle analysis was performed by quantitative fluorescence.

RESULTS

The number of EdU-positive cells, with a median of 11.52 cells (10.47-12.62 cells) in basal conditions, was decreased by all the AEDs except eslicarbazepine (10-300 µM). Number of cells was decreased by 60% after treatment with ESL (30 µM), by 40% after treatment with R-Licarbazepine (1 µM), between 65-75% after treatment with CBZ (10-300 µM), by 60% or 90% after treatment with OXC (30-300 µM), by 30% after treatment with LTG (300 µM), and by 98% after treatment with VPA (1-3 mM) (figure 1).

Cells in G0/G1 phase increased by 2% after treatment with LTG (10 µM) and by 13% after treatment with VPA (1 mM) (figure 2).

The number of cells in S phase was unchanged by the AEDs [median of 3.4% (2.6-4.0%)].

However, the number of cells in G2/M phase was increased by 90% after exposure to OXC (300 µM), while VPA (1-3 mM) decreased the number of G2/M cells by 65-70% (figure 3).

RESULTS

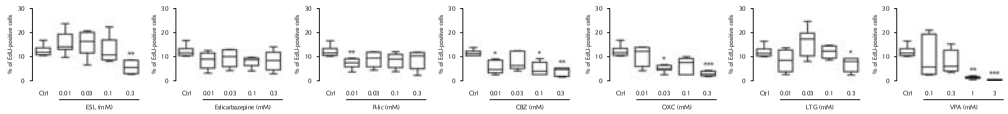


Figure 1 – Effects of AED exposure on EdU incorporation in neural stem cells cultures of rat SVZ.

Notes: EdU incorporation was assessed by flow cytometry analysis after exposure to AEDs (24 h). Data are expressed in boxplots as medians and inter-quartiles range of at least 3 independent experiments. Kruskal-Wallis analyses of non-parametric data were followed by Dunn's selected pairs of columns. ESL, eslicarbazepine acetate; R-lic, R-licarbazepine; CBZ, carbamazepine; OXC, oxcarbazepine; LTG, lamotrigine; VPA, valproic acid; *, p<0.05; **, p<0.01 ; ***, p<0.001.

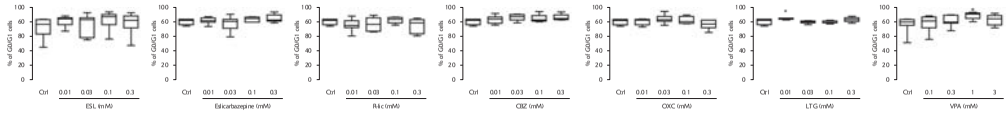


Figure 2 – Effects of AED exposure on the percentage of cells in G0/G1 phase in neural stem cells cultures of rat SVZ.

Notes: DNA content was assessed by measuring 7-AAD flourescence, by flow cytometry analysis, after exposure to AEDs (24 h). Data are expressed in boxplots as medians and inter-quartiles range of at least 3 independent experiments. Kruskal-Wallis analyses of non-parametric data were followed by Dunn's selected pairs of columns. ESL, eslicarbazepine acetate; R-lic, R-licarbazepine; CBZ, carbamazepine; OXC, oxcarbazepine; LTG, lamotrigine; VPA, valproic acid; *, p<0.05.

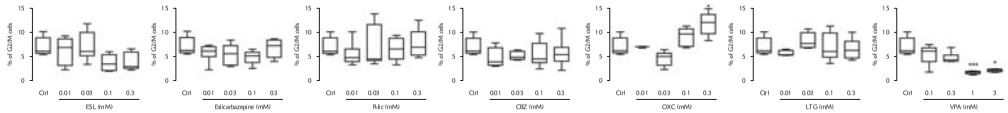


Figure 3 – Effects of AED exposure on the percentage of cells in G2/M phase in neural stem cells cultures of rat SVZ.

Notes: DNA content was assessed by measuring 7-AAD flourescence, by flow cytometry analysis after exposure to AEDs (24 h). Data are expressed in boxplots as medians and inter-quartiles range of at least 3 independent experiments. Kruskal-Wallis analyses of non-parametric data were followed by Dunn's selected pairs of columns. ESL, eslicarbazepine acetate; R-lic, R-licarbazepine; CBZ, carbamazepine; OXC, oxcarbazepine; LTG, lamotrigine; VPA, valproic acid; *, p<0.05; ***, p<0.001.

CONCLUSION

Eslicarbazepine, the major human metabolite of ESL, does not alter the proliferation of neural stem cells, whereas CBZ, OXC and VPA impaired proliferation of neural stem cells.

REFERENCES

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

The effects of eslicarbazepine on receptors, ion channels, enzymes and transporters

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PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization. (1)

This study was aimed to determine the interaction of eslicarbazepine, the main active metabolite of ESL, with potential biological targets.

METHODS

Displacement of binding of specific ligands or substrates for 95 human G-protein coupled and ligand gated receptors, ion channels, enzymes and transporters was tested in the presence of 400 µM eslicarbazepine.

Some electrophysiological experiments were conducted with mouse N1E-115 cells and transfected cells expressing human $Ca_v3.2$ channels.

Cell lines: Used HEK 293 cells stably transfected with the human $Ca_v3.2$ cDNA and N1E-115 cells.

Electrophysiological Recordings: Cells were continuously perfused with bath solution. Calcium inward currents in HEK 293 cells were measured upon depolarization of the cell membrane. Once control recordings were accomplished, cells were perfused with bath solution containing eslicarbazepine (0.3 to 1000 µM) or the reference compound valproic acid (1 mM).

To determine the fast and slow inactivation tetrodotoxin sensitive sodium currents in N1E-115 cell the whole cell configuration was tested and voltage protocol was applied under control conditions and in the steady state during perfusion of 250 µM eslicarbazepine.

Data Analysis: All calculations and data fittings were done using SigmaPlot. Data represent means ± standard error of the mean (SEM).

RESULTS

In the presence of 400 µM eslicarbazepine, no relevant interactions were observed with receptors, ion channels, enzymes and transporters (table 1).

Eslicarbazepine does not alter fast inactivation of voltage-gated sodium channel (VGSC) as observed in figure 1 but reduced VGSC availability through enhancement of slow inactivation (figure 2 and 3) with an affinity to the slow inactivated state 5.9 times higher than to the channels in the resting state (table 2).

Eslicarbazepine dependently inhibited $Ca_v3.2$ calcium peak currents (figure 4). The inhibition curve was best fitted with a two site binding model and constant remaining current amplitude. A block of high affinity occurs with an IC_{50} of 0.4 µM and a block occurs at higher concentrations of the test items, with an IC_{50} of 62.6 µM. Regarding the reference compound, 1 mM valproic acid blocked calcium peak currents by 66.15 ± 2.05 %.

RESULTS

Table 1 – Summary of the *in vitro* selectivity profile for eslicarbazepine against the Caliper Life Sciences General Side Effect Explorer Panel

Receptor/ion channel/enzyme/transporter	% Inhibition at 400 µM	Receptor/ion channel/enzyme/transporter	% Inhibition at 400 µM
Adenosine Transporter (h)	10.13	Serotonin, 5HT6 (h)	5.86
Adenosine, A1 (h)	32.34	Serotonin, 5HT7 (h)	0.0
Adenosine, A2	0.0	Sigma 1	28.43
Adenosine, A2A (h)	6.81	Sigma 2	6.11
Adrenergic, Alpha 2A (h)	15.62	Inositol Triphosphate, IP3	0.45
Cannabinoid, CB1 (h)	20.44	Nitric Oxide, NOS (Neuronal-Binding)	0.0
Dopamine Transporter (h)	2.85	Calcium Channel, Type N	23.34
Dopamine, D1 (h)	6.85	GABA, Chloride, TBOB Site	38.95
Dopamine, D2s (h)	0.0	Potassium Channel, ATP-Sensitive	6.78
Dopamine, D3	0.0	Sodium, Site 2	34.46
Dopamine, D4.2 (h)	0.0	Corticotropin Releasing Factor, Non-selective	26.95
Dopamine, D4.4 (h)	0.0	Thyrotropin Releasing Hormone, TRH	16.14
GABA A, Agonist Site	0.0	Angiotensin II, AT2	11.32
GABA A, BDZ, alpha 1 site	25.92	Cholecystokinin, CCK2 (CCKB)	32.83
GABA A, BDZ, alpha 5 site	23.75	Galanin, Non-Selective	6.11
GABA A, BDZ, alpha 6 site	0.0	Neurokinin, NK1	12.58
GABA-B	11.72	Neurokinin, NK3 (NKB)	0.0
Glutamate, AMPA Site (Ionotropic)	0.0	Neuropeptide, NPY2 (h)	8.43
Glutamate, Chloride Dependent Site (Ionotropic)	9.36	Neurotensin (h)	4.94
Glutamate, Kainate Site (Ionotropic)	1.56	Somatostatin, Non-selective	0.0
Glutamate, MK-801 Site (Ionotropic)	15.45	Anhydrase, Carbonic, Isozyme I (h)	27.74
Glutamate, NMDA Agonist Site (Ionotropic)	0.0	Anhydrase, Carbonic, Isozyme II (h)	5.93
Glutamate, NMDA, Phencyclidine Site (Ionotropic)	0.0	Decarboxylase, Glutamic Acid	0.0
Glutamate, mGluR1 (Metabotropic)	1.82	Esterase, Acetylcholine (h)	0.0
Glutamate, mGluR5 (Metabotropic)	14.42	Oxidase, MAO-A, Central	15.98
Glutamate,NMDA,Glycine (Stry-insens Site) (Ionot)	13.21	Oxidase, MAO-B, Central	0.95
Glycine, Strychnine-sensitive	25.95	Oxygenase, COX-2	0.0
Histamine, H1	23.23	Protease, Caspase, CASP-1 (h)	0.0
Histamine, H3	0.0	Protease, Caspase, CASP-10 (h)	0.0
Imidazoline, I2 (Central)	17.45	Protease, Caspase, CASP-2 (h)	0.0
Melatonin, Non-selective	17.43	Protease, Caspase, CASP-3 (h)	0.0
Muscarinic, M1 (hr)	0.0	Protease, Caspase, CASP-8 (h)	0.0
Muscarinic, M4 (h)	6.08	Translerase, Choline Acetyl	0.0
Muscarinic, M5 (h)	15.98	Serotonin, 5HT2C	3.67
Nicotinic, Neuronal (a-BnTx insensitive) (h)	23.46	Kinase, Protein, CK1d (CSNK1D) (h)	5.18
Norepinephrine Transporter (h)	9.33	Kinase, Protein, Fyn (h)	3.58
Opioid, Delta 2 (h)	7.91	Kinase, Protein, GSK3b (h)	4.32
Opioid, Kappa 1	5.39	Kinase, Protein, MAPK1 (ERK2, p42mapk) (h)	0.0
Opioid, Mu (h)	0.0	Kinase, Protein, MAPK3 (ERK1, P44MAPK) (h)	2.05
Purinergic, P2Y	0.0	Kinase, Protein, PKA (h)	3.67
Serotonin Transporter (h)	0.0	Kinase, Protein, PKCb2 (h)	0.0
Serotonin, 5HT1, Non-Selective	11.43	Kinase, Protein, PKCz (h)	1.48
Serotonin, 5HT1A (h)	40.76	Kinase, Protein, ROCK2 (h)	8.54
Serotonin, 5HT1B	45.48	Kinase, Protein, SGK1 (h)	5.70
Serotonin, 5HT1D (h)	16.40	Serotonin, 5HT5A (h)	11.88
Serotonin, 5HT2A (h)	19.22	Serotonin, 5HT4	7.38

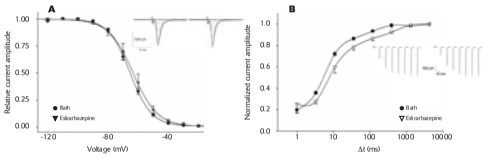

Figure 1 – Fast inactivation A) and recovery from fast inactivation B) in the presence of 250 µM of eslicarbazepine. Insets represent respective current traces for tail currents (left is under control conditions).

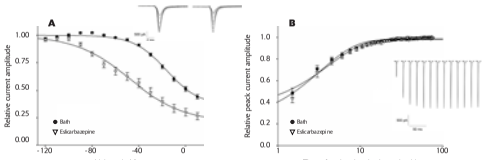

Figure 2 – Slow inactivation A) and recovery from slow inactivation B) in the presence of 250 µM of eslicarbazepine. Insets represent respective current traces for tail currents (left is under control conditions).

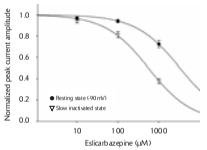

Figure 3 – Concentration response curves from channels in the resting and slow inactivated state.

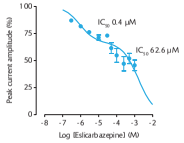

Figure 4 – Inhibition concentration-response curves for the blockade of $Ca_v3.2$ currents by eslicarbazepine. Data represent means ±SEM (n=3-9).

RESULTS

Table 2 – The half maximal inhibitory concentration (IC_{50}) and Hill coefficients from resting and slow inactivated channels

Test Item	IC_{50} value (µM)		Hill coefficient	
	Resting state	Slow inactivated state	Resting state	Slow inactivated state
Eslicarbazepine	3301.59	559.27	0.80	0.82

CONCLUSION

Eslicarbazepine is a selective slow inactivator of VGSC and potent $Ca_v3.2$ blocker devoid of effects upon major G protein coupled and ligand gated receptors, ion channels, enzymes and transporters.

REFERENCES

1. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. Epilepsia 2012;53(6):935-46.

CONTACT INFORMATION

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

The effects of eslicarbazepine, R-licarbazepine, oxcarbazepine, and carbamazepine on sodium currents through $Na_V1.2$ channels

Pires N[1], Brady K[2], Hebeisen S[2] and Soares-da-Silva P[1,3]

[1]BIAL - Portela & Ca. SA, S. Mamede do Coronado, Portugal; [2]B'SYS GmbH, Witterswil, Switzerland; [3]University of Porto, Porto, Portugal

PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1). ESL undergoes rapid and extensive first pass metabolism via hydrolysis to eslicarbazepine, its major active metabolite (1).

This study was aimed to determine the effects of eslicarbazepine, R-licarbazepine (minor metabolite of ESL), oxcarbazepine, and carbamazepine on the rat $Na_V1.2$ sodium channel expressed in chinese-hamster ovary (CHO) cells.

METHODS

Cell lines: CHO cells were transfected with $Na_V1.2$ cDNA to express $rNa_V1.2$ sodium channel currents and used for electrophysiological experiments 24-48 hours later.

Electrophysiological Recordings: The whole-cell patch-clamp technique was used to investigate the effects of eslicarbazepine, R-licarbazepine, oxcarbazepine and carbamazepine on $Na_V1.2$ inward peak currents. Inward peak currents of $rNa_V1.2$ were measured upon depolarization to -10 mV for 10 ms at holding potentials of either -80 mV or -70 mV. The voltage protocol was run at 6 seconds intervals. Once control recordings were obtained, and after reaching steady-state, cells were continuously perfused with bath solution containing eslicarbazepine, R-licarbazepine, oxcarbazepine or carbamazepine (0 – 1000 µM range). The non-selective Na_V blocker tetrodotoxin (0.5 µM) or lidocaine (100 µM) was used as control. Vehicle was DMSO (0.2-0.4%).

Data Analysis: SigmaPlot was used to calculate the Mean ± Standard Error of the Mean (SEM) of relative peak current blockade for each compound. The data was normalized to the control peak current amplitude at the beginning of the experiment.

RESULTS

As shown in tables 1-3 and figure 1, with the exception of carbamazepine, the potency of inhibition was highly sensitive to the holding potential, increasing with depolarization, but the affinity of eslicarbazepine was approximately 2- to 3-fold lower than that of oxcarbazepine and carbamazepine in more depolarized conditions. Carbamazepine was endowed with the potency to inhibit inward $Na_V1.2$ sodium currents at -80 mV and -70 mV holding potentials.

RESULTS

Table 1 – Effect of eslicarbazepine, R-licarbazepine, carbamazepine and oxcarbazepine on relative $rNa_V1.2$ peak currents in transfected CHO cells at a holding potential of -80 mV.

	Relative peak current (%)							
	Eslicarbazepine		R-Licarbazepine		Oxcarbazepine		Carbamazepine	
µM	Mean ± SEM	n	Mean ± SEM	n	Mean ± SEM	n	Mean ± SEM	n
25	N.D.		N.D.		N.D.		93.40±3.81	5
50	96.35±1.53	3	98.03±1.15	4	91.24±4.04	5	76.92±5.48	5
100	88.40±2.16	3	91.42±1.76	4	82.22±7.06	5	54.55± 7.95	5
250	76.37±3.41	3	82.13±2.41	4	67.87±9.34	5	35.63±7.97	5
500	61.64±4.34	3	61.55±3.49	4	51.34±10.38	5	15.48±6.91	5
1000	46.05±2.03	3	43.21±3.08	4	24.82±10.08	5	N.D.	

Notes: Control values varied between 87.93±3.30 % and 100.58±1.41 % (n=3 to 5). Values obtained with blocker tetrodotoxin (0.5 µM) were 2.81±1.01 % (n=3) and with blocker lidocaine (100 µM) values varied between 51.83±5.91 % and 68.79±4.61 % (n=5); N.D.; not determined.

Table 2 – Effect of eslicarbazepine, R-licarbazepine, carbamazepine and oxcarbazepine on relative $rNa_V1.2$ peak currents in transfected CHO cells at a holding potential of -70 mV.

	Relative peak current (%)							
	Eslicarbazepine		R-Licarbazepine		Oxcarbazepine		Carbamazepine	
µM	Mean ± SEM	n	Mean ± SEM	n	Mean ± SEM	n	Mean ± SEM	n
50	88.87±1.47	6	88.04±4.38	5	64.45±4.99	6	76.46±4.00	5
100	64.52±3.69	6	74.83±7.71	5	42.71±7.05	6	60.18±5.34	5
250	46.60±5.67	6	57.62±10.04	5	20.32±5.25	6	30.13±4.61	5
500	32.14±7.36	6	40.76±9.10	5	12.13±4.99	6	8.66±2.15	5
1000	17.11±6.80	6	25.05±6.84	5	2.13±1.63	6	0.61±0.32	5

Notes: Control values were 91.29±2.64 % (n=5). Values obtained with blocker lidocaine (100 µM) were 50.72±8.76 % (n=5).

Table 3 – Half-maximal inhibitory concentration (IC_{50}) values derived from the inhibition curves at -80 mV and -70 mV holding potentials for eslicarbazepine, R-licarbazepine, oxcarbazepine and carbamazepine.

	IC_{50} (µM)	
Test Items	-80 mV	-70 mV
Eslicarbazepine	829.45	224.0
R-Licarbazepine	780.01	334.9
Oxcarbazepine	455.72	80.53
Carbamazepine	161.67	126.7

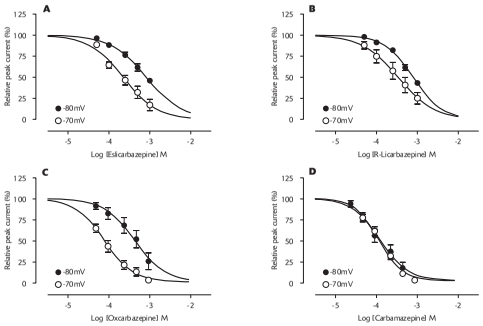

Figure 1 – Inhibition concentration response curves by eslicarbazepine (A), R-licarbazepine (B), oxcarbazepine (C) and carbamazepine (D) on the $rNa_V1.2$ currents from transfected CHO cells at holding potentials of -80 mV and -70 mV. Results are means ± SEM (n=3-6).

CONCLUSION

Eslicarbazepine demonstrated a greater selectivity for the inactive state of $Na_V1.2$ sodium channels, which is the common feature of the rapidly firing neurons, over their resting state as compared to carbamazepine and oxcarbazepine.

REFERENCES

1. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. Epilepsia 2012;53(6):935-46.

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

The effects of eslicarbazepine, R-licarbazepine, oxcarbazepine and carbamazepine on sodium currents through $Na_v1.3$ channels

Wright LC[1], Brady K[2], Hebeisen S[2] and Soares-da-Silva P[1,3]

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PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1).

ESL undergoes rapid and extensive first pass metabolism via hydrolysis to eslicarbazepine, its major active metabolite, which blocks voltage-gated sodium- and calcium-channels (1).

This study was aimed to determine the effects of eslicarbazepine, R-licarbazepine (minor metabolite of ESL), oxcarbazepine (OXC) and carbamazepine (CBZ) on the human $Na_v1.3$ sodium channel expressed in Chinese-hamster ovary (CHO) cells.

METHODS

Cell lines: CHO were transfected with human $Na_v1.3$ sodium channel cDNA and used for electrophysiological experiments 24-48 hours later.

Electrophysiological Recordings: To evaluate the inhibitory potencies the $Na_v1.3$ inward peak currents were measured upon depolarization of the cell membrane for 10 ms to -10 mV at holding potentials of either -80 mV or -60 mV. Once control recordings were obtained, and after reaching steady-state, cells were perfused with bath solution containing eslicarbazepine, R-licarbazepine or OXC (0-1000 µM) or CBZ (0-500 µM). As control tetrodotoxin (TTX), a non selective Na_v blocker, was used at 0.5 µM. Vehicle was DMSO (0.2-0.4%).

To determine the affinities for the resting and inactivate states of $hNa_v1.3$ channels, $Na_v1.3$ inward peak currents were measured upon depolarization to 0 mV for 10 ms from a holding potential of −100 mV. Once sodium current levels were constant, an inactivation curve was recorded. Cells were depolarized to 0 mV after 15 s conditioning prepulses ranging from −120 mV to −30 mV. Cells were then perfused with bath solution containing the eslicarbazepine, R-licarbazepine, OXC or CBZ (250 µM).

Data Analysis: All calculations and data fittings were made using SigmaPlot. Data is presented as means ± standard error of the mean (SEM).

RESULTS

The whole-cell patch-clamp technique was used to investigate the effects of eslicarbazepine, R-licarbazepine, OXC and CBZ on $Na_v1.3$ inward peak currents.

As shown in table 1 and figure 1 the potency of inhibition was highly sensitive to the holding potential, increasing with depolarisation. The affinity of eslicarbazepine was, however, approximately 3-fold lower than that of CBZ and OXC in more depolarized conditions.

All compounds, as shown in figure 2 and table 2, demonstrated a much higher affinity for the inactivated (K_i) state of the channel, but the affinity of eslicarbazepine and R-licarbazepine for voltage-gated sodium channels in the resting (K_r) state was about 2-fold lower than that of CBZ and OXC.

RESULTS

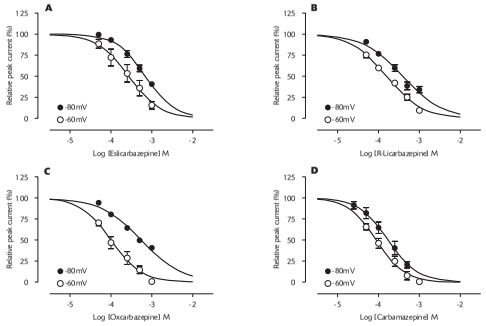

Figure 1 – Inhibition concentration response curves by eslicarbazepine (A), R-licarbazepine (B), oxcarbazepine (C) and carbamazepine (D) on the $hNa_v1.3$ currents from transfected CHO cells at holding potentials of -80 mV and -60 mV. Results are means ± SEM (n=3-5).

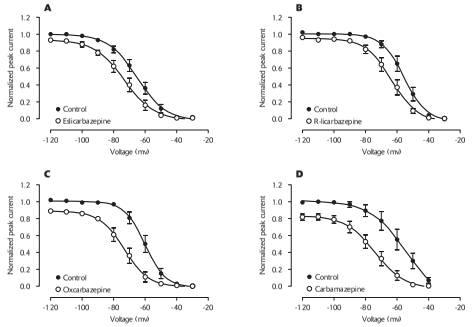

Figure 2 – Curve fits for the determination of the affinities for the resting (K_r) and inactivated states (K_i) of the $hNa_v1.3$ channels from transfected CHO cells for 250 µM of eslicarbazepine (A), R-licarbazepine (B), oxcarbazepine (C) or carbamazepine (D). Results are means ± SEM (n=5-7).

Table 1 – Half maximal inhibitory concentration (IC_{50}) values derived from the inhibition curves at -80 mV and -60 mV holding potentials for eslicarbazepine, R-licarbazepine, oxcarbazepine and carbamazepine.

	IC_{50} (µM)	
Test Items	-80 mV	-60 mV
Eslicarbazepine	703.86	267.7
R-Licarbazepine	383.35	158.4
Oxcarbazepine	549.48	99.50
Carbamazepine	187.67	90.20

Table 2 – Affinities of eslicarbazepine, R-licarbazepine, oxcarbazepine and carbamazepine to the resting state (K_r) and inactivated state (K_i) of $hNa_v1.3$ sodium channels expressed in CHO cells.

Test Items	K_r (Means±SEM) µM	K_i (Means±SEM) µM
Eslicarbazepine	4813.25±1136.16 (n=6)	165.39 ± 26.80 (n=6)
R-Licarbazepine	5376.55± 1021.86 (n=6)	96.50 ± 23.55 (n=7)
Oxcarbazepine	1870.42 ± 199.72 (n=6)	29.81 ± 8.12 (n=6)
Carbamazepine	1535.94 ± 346.37 (n=5)	30.07 ± 6.60 (n=5)

CONCLUSION

Eslicarbazepine demonstrated a greater selectivity for the inactive state of $Na_v1.3$ sodium channels, which is the common feature of the rapidly firing neurons, over their resting state as compared to CBZ and OXC.

REFERENCES

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Effects of eslicarbazepine, R-licarbazepine and oxcarbazepine on fast and slow inactivation of voltage-gated sodium channels

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PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1).

Eslicarbazepine, the major (94.5%) active metabolite of ESL, preferentially enhances the slow inactivation of voltage-gated sodium channels (VGSC).

This study was aimed to compare the effects of eslicarbazepine with the effects of R-licarbazepine and oxcarbazepine (OXC), two minor metabolites (5.0% and 0.5%, respectively) of ESL, on the fast and slow inactivated states of VGSC.

METHODS

Cell lines: Used N1E-115 mouse neuroblastoma cells.

Electrophysiological Recordings: Sodium inward tail currents were measured upon depolarization of the cell membrane to -10 mV for 10 ms. Once control recordings were obtained, cells were perfused with bath solution containing eslicarbazepine or R-licarbazepine or OXC.

Fast inactivation curves were obtained by depolarizing cells to potentials between -120 mV and 0 mV, followed by a 10 ms test pulse to -10 mV before stepping back to -80 mV.

The recovery from the fast inactivated state was analyzed with a test pulse of 20 ms to -10 mV, then after 100 ms at the resting potential of -90 mV cells were depolarized to -10 mV. After a variable pulse to -90 mV a second test pulse was applied.

For slow inactivation curve determination, cells were depolarized to potentials between -120 mV and +50 mV, followed by a 1 s pulse to -80 mV and a test pulse to -10 mV before stepping back to -80 mV.

To evaluate the IC_{50} in the slow inactivated state, a test pulse of 20 ms to -10 mV was applied, then after 1.5 s at the resting potential of -90 mV cells were depolarized for 10 s to -20 mV. After a 1.5 s pulse to -80 mV a second test pulse was applied, in the presence of various concentrations of either eslicarbazepine or LCS.

To determine the time constant of the physiological entry of the sodium channels into the slow inactivated state different pulse durations for the long depolarizing voltage pulse to -20 mV were analyzed at 250 µM of either eslicarbazepine or R-licarbazepine or OXC.

Data Analysis: All calculations and data fittings were performed with SigmaPlot. Data is presented as means ± standard error of the mean (SEM).

RESULTS

The whole-cell patch-clamp technique was used to investigate the effects of eslicarbazepine, R-licarbazepine and OXC (all at 250 µM) on sodium channels endogenously expressed in N1E-115 cells, in conditions of fast and slow inactivation of sodium currents.

Steady state fast inactivation curves (table 1 and figure 1) were shifted in the hyperpolarizing direction by OXC (-17 mV), but not by eslicarbazepine (-3.54 mV) or R-licarbazepine (-0.65 mV).

RESULTS

Table 1 – Midpoint of the inactivation curve ($V_{0.5}$) values obtained from fast and slow inactivation curves

	$V_{0.5}$ Mean ± SEM	
Test Item (250 µM)	Fast inactivation	Slow inactivation
Control (Bath)	-68.66 ± 0.84 mV (n=29)	-16.21 ± 1.21 mV (n=13)
Eslicarbazepine	-65.12 ± 2.15 mV (n=5)	-47.37 ± 3.15 mV (n=6)
R-licarbazepine	-68.01 ± 2.02 (n=7)	-48.12 ± 2.71 (n=4)
Oxcarbazepine	-85.24 ± 1.54 mV (n=4)	-44.27 ± 1.92 (n=4)

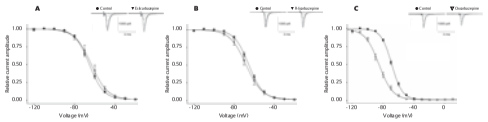

Figure 1 – Fast inactivation curves obtained in the presence of 250 µM of eslicarbazepine (A), R-licarbazepine (B) or oxcarbazepine (C). Results are means ± SEM (n=4-29). Insets depict the respective representative tail current traces.

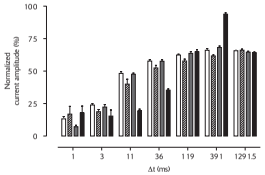

Figure 2 – Recovery from fast inactivated state in control conditions (white bars) or in the presence of 250 µM of eslicarbazepine (hatchet bars) or R-licarbazepine (grey bars) or oxcarbazepine (black bars). The relative current amplitudes were normalized to the current amplitude of the longest recovery time (4262 ms). Results are means ± SEM (n=3-16).

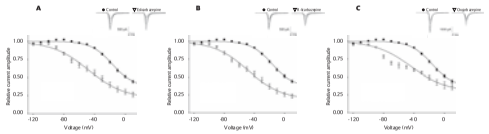

Figure 3 – Slow inactivation curves obtained in the presence of 250 µM eslicarbazepine (A) or R-licarbazepine (B) or oxcarbazepine (C). Results are means ± SEM (n=4-13). Insets depict respective representative tail current traces.

Table 2 – Half maximal inhibitory concentration (IC_{50}) values obtained from resting and slow inactivated channels

	IC_{50} value (µM)	
Test Item	Resting state	Slow inactivated state
Eslicarbazepine	3301.59	559.27
R-licarbazepine	3441.44	590.85
Oxcarbazepine	776.11	424.31

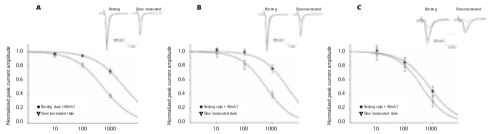

Figure 4 – Concentration response curves obtained from channels in the resting (dark circles) and slow inactivated state (open triangles) in the presence of eslicarbazepine (A), R-licarbazepine (B) or oxcarbazepine (C). Results are means ± SEM (n=3). On the right are depicted the respective representative current traces.

RESULTS

OXC-treated fast inactivated channels required long pulses to recover (Δt = 391 ms), whereas eslicarbazepine- and R-licarbazepine-treated fast inactivated channels recovered similarly to control conditions (Δt = 11 ms) as shown in figure 2.

The voltage dependence of the slow inactivation (shift $V_{0.5}$) for OXC, R-licarbazepine, and eslicarbazepine was -28.1, -31.9, and -31.2 mV, respectively (table 1 and figure 3).

For eslicarbazepine, R-licarbazepine and OXC the affinity to the slow inactivated state was 5.9, 5.8, and 1.8 times higher than to the channels in the resting state, respectively (table 2 and figure 4).

For eslicarbazepine, R-licarbazepine and OXC, the time constants for entering the slow inactivated state were 7.00, 7.03, and 12.36 s, respectively.

CONCLUSION

Both eslicarbazepine and R-licarbazepine preferentially enhance the slow inactivation of VGSC, whereas OXC appears to modify kinetics and voltage-dependence of fast inactivation states.

REFERENCES

1. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. Epilepsia 2012;53(6):935-46.

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

Effects of eslicarbazepine and lacosamide on slow and fast inactivation of voltage-gated sodium channels

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[1]BIAL - Portela & Ca. SA, S. Mamede do Coronado, Portugal; [2]B'SYS GmbH, Witterswil, Switzerland; [3]University of Porto, Porto, Portugal

PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1).

This study was aimed to determine the effects of eslicarbazepine, the major active metabolite of ESL, and lacosamide (LCS) on the fast and slow inactivated states of voltage-gated sodium channels (VGSC).

METHODS

Cell lines: Used N1E-115 mouse neuroblastoma cells.

Electrophysiological Recordings: Sodium inward tail currents were measured upon depolarization of the cell membrane to -10 mV for 10 ms. Once control recordings were obtained, cells were perfused with bath solution containing eslicarbazepine or LCS.

Fast inactivation curves were obtained by depolarizing cells to potentials between -120 mV and 0 mV, followed by a 10 ms test pulse to -10 mV before stepping back to -80 mV.

The recovery from the fast inactivated state was analyzed with a test pulse of 20 ms to -10 mV, then after 100 ms at the resting potential of -90 mV cells were depolarized to -10 mV. After a variable pulse to -90 mV a second test pulse was applied.

For slow inactivation curve determination, cells were depolarized to potentials between -120 mV and +50 mV, followed by a 1 s pulse to -80 mV and a test pulse to -10 mV before stepping back to -80 mV.

To evaluate the IC_{50} in the slow inactivated state, a test pulse of 20 ms to -10 mV was applied, then after 1.5 s at the resting potential of -90 mV cells were depolarized for 10 s to -20 mV. After a 1.5 s pulse to -80 mV a second test pulse was applied, in the presence of various concentrations of either eslicarbazepine or LCS.

To determine the time constant of the physiological entry of the sodium channels into the slow inactivated state different pulse durations for the long depolarizing voltage pulse to -20 mV were analyzed at 250 µM of either eslicarbazepine or LCS.

Data Analysis: All calculations and data fittings were performed with SigmaPlot. Data is presented as means ± standard error of the mean (SEM).

RESULTS

The whole-cell patch-clamp technique was used to investigate the effects of eslicarbazepine and LCS (both at 250 µM) on sodium channels endogenously expressed in N1E-115 cells, in conditions of fast and slow inactivation of sodium currents.

The shift of steady state fast inactivation curves in the hyperpolarizing direction by LCS (-4.76 mV) was twice that by eslicarbazepine (-3.54 mV) as shown in table 1 and figure 1.

Regarding the recovery of fast inactivated channels, eslicarbazepine- and LCS-treated fast-inactivated channels recovered similarly to control conditions (figure 2).

RESULTS

Table 1 – Midpoint of the inactivation curve ($V_{0.5}$) values obtained from fast and slow inactivation curves

	$V_{0.5}$ Mean ± SEM	
Test Item (250 µM)	Fast inactivation	Slow inactivation
Control (Bath)	-68.66 ± 0.84 mV (n=29)	-16.21 ± 1.21 mV (n=13)
Eslicarbazepine	-65.12 ± 2.15 mV (n=5)	-47.37 ± 3.15 mV (n=6)
Lacosamide	-73.42 ± 2.72 mV (n=5)	-69.49 ± 1.26 mV (n=5)

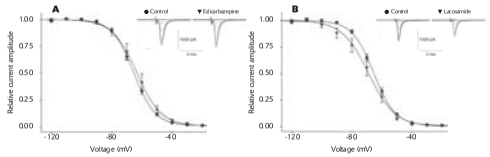

Figure 1 – Fast inactivation curves obtained in the presence of 250 µM of eslicarbazepine (A) or lacosamide (B). Results are means ± SEM (n=5-29). Insets depict the respective representative tail current traces.

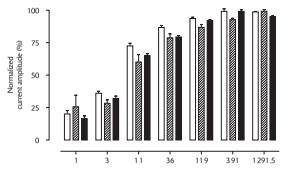

Figure 2 – Recovery from fast inactivated state in control conditions (white bar) or in the presence of 250 µM of eslicarbazepine (hatchet bars) or lacosamide (black bars). The relative current amplitudes were normalized to the current amplitude of the longest recovery time (4262 ms). Results are means ± SEM (n=3-16).

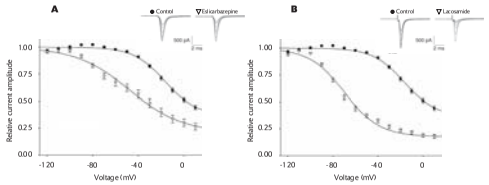

Figure 3 – Slow inactivation curves obtained in the presence of 250 µM eslicarbazepine (A) or lacosamide (B). Results are means ± SEM (n=5-13). Insets depict respective representative tail current traces.

Table 2 – Half maximal inhibitory concentration (IC_{50}) values obtained from resting and slow inactivated channels

	IC_{50} value (µM)	
Test Item	Resting state	Slow inactivated state
Eslicarbazepine	3301.59	559.27
Lacosamide	1889.19	181.75

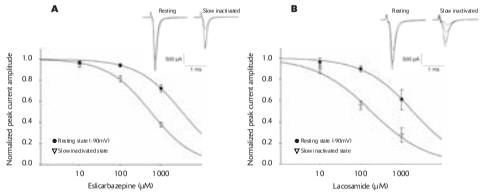

Figure 4 – Concentration response curves obtained from channels in the resting (dark circles) and slow inactivated state (open triangles) in the presence of eslicarbazepine (A) or lacosamide (B). Results are means ± SEM (n=3). On the right are depicted the respective representative current traces.

RESULTS

Eslicarbazepine and LCS shifted the voltage dependence of the slow inactivation ($V_{0.5}$) by -31.2 mV and -53.3 mV, respectively (table 1 and figure 3).

For eslicarbazepine and LCS, the affinity to the slow inactivated state was 5.9 and 10.4 times higher than to the channels in the resting state, respectively (table 2 and figure 4). However, the affinity of LCS (1889 µM) for the channels in the resting state was twice that of eslicarbazepine (3302 µM).

The time constants determined for eslicarbazepine and LCS, for entering the slow inactivated state were 7.00 and 4.54 s, respectively.

CONCLUSION

Both eslicarbazepine and LCS reduce VGSC availability through enhancement of slow inactivation, but LCS demonstrated higher interaction with VGSC in the resting state, with fast inactivation gating and shorter time to enter in the slow inactivated state.

REFERENCES

1. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. Epilepsia 2012;53(6):935-46.

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

Slow and fast inactivation of voltage-gated sodium channels by eslicarbazepine and carbamazepine

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PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1).

No differences in ESL efficacy were observed in patients whose concomitant antiepileptic therapy included carbamazepine (CBZ) (approximately 60% of patients) compared to patients not co-treated with CBZ. The explanation for the efficacy of ESL as an adjunctive therapy in patients refractory to CBZ is certainly multifactorial, but may relate to different pharmacodynamic effects upon voltage-gated sodium channel (VGSC) (2, 3).

This study was aimed to determine the effects of eslicarbazepine, the major active metabolite of ESL, and CBZ on the fast and slow inactivated states of VGSC.

METHODS

Cell lines: Used N1E-115 mouse neuroblastoma cells.

Electrophysiological Recordings: Sodium inward tail currents were measured upon depolarization of the cell membrane to -10 mV for 10 ms. Once control recordings were obtained, cells were perfused with bath solution containing eslicarbazepine or CBZ.

Fast inactivation curves were obtained by depolarizing cells to potentials between -120 mV and 0 mV, followed by a 10 ms test pulse to -10 mV before stepping back to -80 mV.

The recovery from the fast inactivated state was analyzed with a test pulse of 20 ms to -10 mV, then after 100 ms at the resting potential of -90 mV the cell was depolarized for 500 ms to -10 mV. After a variable pulse to -90 mV a second test pulse was applied.

For slow inactivation curve determination, cells were depolarized to potentials between -120 mV and +50 mV, followed by a 1 s pulse to -80 mV and a test pulse to -10 mV before stepping back to -80 mV.

To evaluate the IC_{50} in the slow inactivated state, a test pulse of 20 ms to -10 mV was applied, then after 1.5 s at the resting potential of -90 mV the cell was depolarized to -20 mV. After a 1.5 s pulse to -80 mV a second test pulse was applied, in the presence of various concentrations of either eslicarbazepine or CBZ.

To determine the time constant of the physiological entry of the sodium channels into the slow inactivated state different pulse durations for the long depolarizing voltage pulse to -20 mV were analyzed at 250 µM of either eslicarbazepine or CBZ.

Data Analysis: All calculations and data fittings were done using SigmaPlot. Data is presented as means ± standard error of the mean (SEM).

RESULTS

The whole-cell patch-clamp technique was used to investigate the effects of eslicarbazepine and CBZ (both at 250 µM) on sodium channels endogenously expressed in N1E-115 cells, in conditions of fast and slow inactivation of sodium currents.

Steady state fast inactivation curves (table 1, figure 1) were shifted in the hyperpolarizing direction by CBZ (-7 mV), but not by eslicarbazepine (-3.54 mV).

RESULTS

Table 1 – Midpoint of the inactivation curve ($V_{0.5}$) values obtained from fast and slow inactivation curves.

	$V_{0.5}$ Mean ± SEM	
Test Item (250 µM)	Fast inactivation	Slow inactivation
Control (Bath)	-68.66 ± 0.84 mV (n=29)	-16.21 ± 1.21 mV (n=13)
Eslicarbazepine	-65.12 ± 2.15 mV (n=5)	-47.37 ± 3.15 mV (n=6)
Carbamazepine	-75.66 ± 2.66 mV (n=6)	-20.84 ± 1.97 mV (n=4)

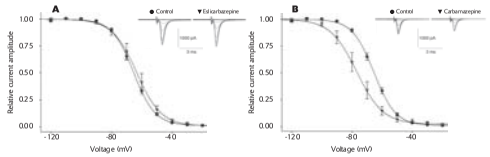

Figure 1 – Fast inactivation curves obtained in the presence of 250 µM eslicarbazepine (A) or 250 µM carbamazepine (B). Results are means ± SEM (n=5-29). Insets depict respective representative tail current traces.

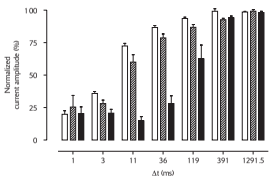

Figure 2 – Recovery from fast inactivated state in control conditions (white bars) or in the presence of 250 µM of eslicarbazepine (hatchet bars) or carbamazepine (black bars). The relative current amplitudes were normalized to the current amplitude of the longest recovery time (4262 ms). Results are means ± SEM (n=3-16).

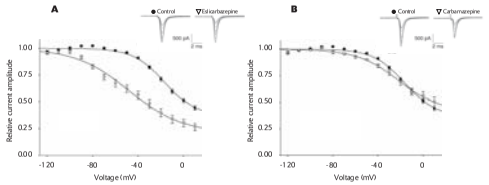

Figure 3 – Slow inactivation curves obtained in the presence of 250 µM eslicarbazepine (A) or carbamazepine (B). Results are means ± SEM (n=4-13). Insets depict respective representative tail current traces.

Table 2 – Half maximal inhibitory concentration (IC_{50}) values obtained from resting and slow inactivated channels.

	IC_{50} value (µM)	
Test Item	Resting state	Slow inactivated state
Eslicarbazepine	3301.59	559.27
Carbamazepine	459.71	263.08

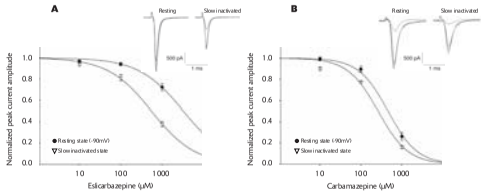

Figure 4 – Concentration response curves obtained from channels in the resting (dark circles) and slow inactivated state (open triangles) in the presence of eslicarbazepine (A) and carbamazepine (B). Results are means ± SEM (n=3). On the right are depicted the respective representative current traces.

RESULTS

The fast-inactivated channels treated with eslicarbazepine recovered similarly to control conditions (Δt = 11 ms), whereas CBZ-treated channels required longer pulses to recover (Δt = 391 ms) as shown in figure 2.

Regarding slow inactivation, CBZ shifted by -4.6 mV the voltage dependence of the slow inactivation, whereas for eslicarbazepine the shift $V_{0.5}$ was -31.2 mV (table 1, figure 3).

The affinity of eslicarbazepine to the slow inactivated state was 5.9 higher than to the channels in the resting state whereas the affinity of CBZ was 1.7 time higher to the slow inactivated state than to the resting state (table 2, figure 4).

The time constants determined for eslicarbazepine and CBZ, for entering the slow inactivated state were 7.00 and 14.49 s, respectively.

CONCLUSION

Eslicarbazepine does not share with CBZ the ability to alter fast inactivation of VGSC, but rather appears to modify the kinetics and voltage-dependence of slow inactivation states.

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1. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. Epilepsia 2012;53(6):935-46.
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CONTACT INFORMATION

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

The effects of eslicarbazepine and R-licarbazepine on sodium currents through $Na_v1.7$ and $Na_v1.8$ channels

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PURPOSE

Eslicarbazepine is the major active metabolite of eslicarbazepine acetate (ESL), a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1).

This study was aimed to determine the effects of eslicarbazepine and R-licarbazepine on the human $Na_v1.7$ and $Na_v1.8$ sodium channels expressed in Chinese-hamster ovary (CHO) cells.

METHODS

Cell lines: CHO cells were transfected with human $Na_v1.7$ sodium channel cDNA and ND7/23 neuroblastoma x rat neuron hybrid cells were transfected with human $Na_v1.8$ sodium channel cDNA. Cells were used for electrophysiological experiments 24-48 hours later.

Electrophysiological Recordings: For inhibitory potency evaluation $Na_v1.7$ and $Na_v1.8$ inward peak currents were measured upon depolarization of the cell membrane for 10 ms to -10 mV ($Na_v1.7$) or for 50 ms to 0 mV ($Na_v1.8$) at the holding potential of -80 mV. Once control recordings were obtained and after reaching steady-state, cells were perfused with bath solution containing eslicarbazepine or R-licarbazepine. As controls, the non-selective Na_v blocker tetrodotoxin (0.5 µM) was used for $Na_v1.7$ and the channel blocker tetracaine (0.1 µM) was used for $Na_v1.8$. Vehicle was DMSO 0.2%.

To determine the affinities for the resting and inactivate states of $hNa_v1.7$ and $hNa_v1.8$ channels, inward peak currents were measured upon depolarization to 0 mV for 10 ms from a holding potential of −100 mV. Once sodium current levels were constant, an inactivation curve was recorded. For $hNa_v1.7$ cells were depolarized to 0 mV after 15 s conditioning prepulses ranging from −120 mV to −40 mV and for $Na_v1.8$ cells were depolarized to 0 mV after 500 ms conditioning prepulses ranging from −120 mV to 0 mV. Cells were then perfused with bath solution containing the eslicarbazepine or R-licarbazepine (250 µM).

Data Analysis: All calculations and data fittings were made using SigmaPlot. Data is presented as means ± standard error of the mean (SEM).

RESULTS

The whole-cell patch-clamp technique was used to investigate the effects of eslicarbazepine and R-licarbazepine on $Na_v1.7$ and $Na_v1.8$ inward peak currents.

At -80 mV holding potential, eslicarbazepine and R-licarbazepine were equipotent in inhibiting inward sodium currents through $Na_v1.7$ and $Na_v1.8$ channels (table 1, figure 1).

As shown in table 2, the affinity of eslicarbazepine and R-licarbazepine for the inactivated (K_i) state of $Na_v1.7$ was about 10 fold higher than that for $Na_v1.8$ channels; and the affinity of eslicarbazepine for both channels is about 2 fold higher than that of R-licarbazepine.

On the other hand, both compounds demonstrated a 20-30 times higher affinity for the inactivated (K_i) state versus the resting (K_r) state of the $Na_v1.7$ channels, when compared to $Na_v1.8$ channels (table 2, figure 2).

RESULTS

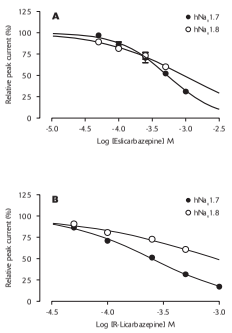

Figure 1 – Inhibition concentration response curves by A) eslicarbazepine and B) R-licarbazepine on the $hNa_v1.7$ currents from transfected CHO cells and $hNa_v1.8$ currents from transfected ND7/23 cells at a holding potential of -80 mV. Results are means ± SEM (n=3-9).

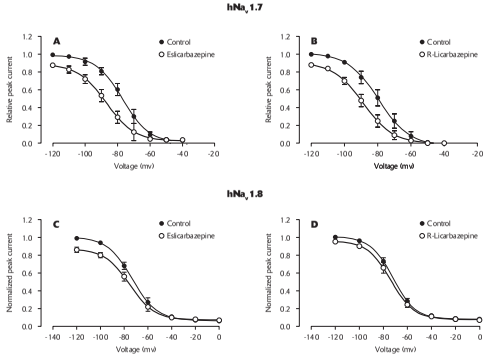

Figure 2 – Curve fits for the determination of the affinities for the rest ing (K_r) and inactivated states (K_i) of the $hNa_v1.7$ channels from transfected CHO cells for 250 µM of eslicarbazepine (A) and R-licarbazepine (B) and of hNav1.8 channels from transfected ND7/23 cells for 250 µM of eslicarbazepine (C) and R-licarbazepine (D). Results are means ± SEM (n=6).

Table 1 – Half maximal inhibitory concentration (IC_{50}) values derived from the inhibition curves for eslicarbazepine and R-licarbazepine on $hNa_v1.7$ and $hNa_v1.8$ channels.

	IC_{50} (µM)	
Test Items	$hNa_v1.7$	$hNa_v1.8$
Eslicarbazepine	523.10	728.42
R-Licarbazepine	246.28	732.48

Table 2 – Affinities of eslicarbazepine and R-licarbazepine to the resting state (K_r) and inactivated state (K_i) of $hNa_v1.7$ sodium channels expressed in CHO cells and of $hNa_v1.8$ sodium channels expressed on ND7/23 cells.

Channel	Test Items	K_R (Means±SEM) µM	K_i (Means±SEM) µM
$hNa_v1.7$	Eslicarbazepine	2529.83 ± 404.00 (n=6)	79.83 ± 10.74 (n=6)
	R-Licarbazepine	2391.25 ± 406.43 (n=6)	117.58 ± 20.17 (n=6)
$hNa_v1.8$	Eslicarbazepine	1986.73 ± 426.26 (n=6)	654.32 ± 65.24 (n=6)
	R-Licarbazepine	4818.81 ± 1064.79 (n=6)	1294.61 ± 85.89 (n=6)

CONCLUSION

Eslicarbazepine is endowed with a greater selectivity for the inactive state of $Na_v1.7$ and $Na_v1.8$ sodium channels, when compared with R-licarbazepine.

REFERENCES

1. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. Epilepsia 2012;53(6):935-46.

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

Steady-state pharmacokinetics and tolerability of eslicarbazepine acetate and oxcarbazepine in healthy volunteers

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PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1).

The objective of this study was to investigate the steady-state pharmacokinetics and assess the tolerability of once-daily (QD) regimen of ESL and twice-daily (BID) regimen of oxcarbazepine (Trileptal®; OXC) in healthy volunteers.

METHODS

This was a single centre, open-label, randomised, three-way crossover study in 12 healthy volunteers.

The study consisted of three 8-day treatment periods separated by a washout period of 10-15 days. In each treatment period the volunteers received either a daily oral dose of ESL 900 mg QD, ESL 450 mg BID (data not shown) or OXC 450 mg BID.

Blood samples for the assay of plasma ESL and its metabolites and OXC and its metabolites were taken at the following times in each treatment period: Day 1 to Day 7 – pre-morning dose; Day 8 – pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 and 96 h post-dose.

Safety was evaluated by monitoring of adverse events, clinical laboratory safety tests, vital signs, 12-lead ECG, and physical examinations, including brief neurological examinations.

RESULTS

Pharmacokinetic assessments were performed in 11 subjects in each of the treatment periods. Safety was assessed in all patients who had been enrolled and taken at least one dose of investigational product (n=12).

ESL plasma level was systematically below the limit of quantification (0.17 µmol/L) at all sampling times.

The plasma concentration versus time profiles for eslicarbazepine, R-licarbazepine and oxcarbazepine over 24h, following the last dose of an 8-day QD 900 mg dose of ESL or BID 450 mg dose of OXC are shown in Figures 1 to 3.

Eslicarbazepine was the major drug entity in plasma, accounting for 94.6% and 81.5% of total exposure with ESL 900 mg QD and OXC 450 mg BID, respectively (Figures 1 – 3 and Table 1).

Eslicarbazepine C_{max} (µmol/L) was 82% higher following ESL QD (87.3) compared to OXC BID (48.0) (Figure 1 and Table 1).

The ratio eslicarbazepine exposure (µmol*h/L)/dose (µmol) was 0.38 (1156.3/3037.3) and 0.27 (968.4/3567.6) for ESL and OXC, respectively, which translates in a 40% increase in efficiency of ESL versus OXC to deliver eslicarbazepine.

ESL was 19% more efficient than OXC to deliver all active moieties.

The C_{max} and extent of exposure to drug entities R-licarbazepine and oxcarbazepine was approximately 4-fold higher with OXC as compared with ESL (Figures 2 – 3 and Table 1).

RESULTS

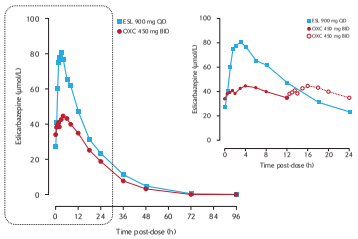

Figure 1 – Mean plasma concentration-time profile of eslicarbazepine following the last dose of an 8-day repeated dosing with ESL 900 mg QD or OXC 450 mg BID to 11 healthy subjects. The inset represents the concentration-time profile of eslicarbazepine up to 24 h following ESL 900 mg QD or OXC 450 mg BID; for OXC 450 mg BID from 12-24 h (red open circles and dotted line) is a duplication of the concentration-time profile from 0-12h as used for the calculation of $AUC_{\tau,0,1}$ over a 24h period. ESL, eslicarbazepine acetate; OXC, oxcarbazepine; BID, twice-daily; QD, once-daily.

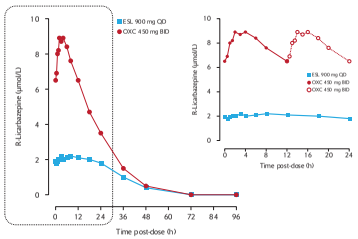

Figure 2 – Mean plasma concentration-time profile of R-licarbazepine following the last dose of an 8-day repeated dosing with ESL 900 mg QD or OXC 450 mg BID to 11 healthy subjects. The inset represents the concentration-time profile of R-licarbazepine up to 24 h following ESL 900 mg QD or OXC 450 mg BID; for OXC 450 mg BID from 12-24 h (red open circles and dotted line) is a duplication of the concentration-time profile from 0-12h as used for the calculation of $AUC_{\tau,0,1}$ over a 24h period. ESL, eslicarbazepine acetate; OXC, oxcarbazepine; BID, twice-daily; QD, once-daily.

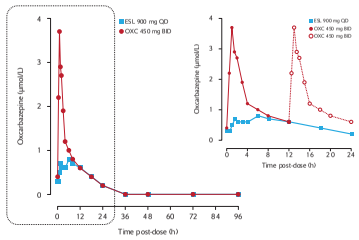

Figure 3 – Mean plasma concentration-time profile of oxcarbazepine following the last dose of an 8-day repeated dosing with ESL 900 mg QD or OXC 450 mg BID to 11 healthy subjects. The inset represents the concentration-time profile of oxcarbazepine up to 24 h following ESL 900 mg QD or OXC 450 mg BID; for OXC 450 mg BID from 12-24 h (red open circles and dotted line) is a duplication of the concentration-time profile from 0-12h as used for the calculation of $AUC_{\tau,0,1}$ over a 24h period. ESL, eslicarbazepine acetate; OXC, oxcarbazepine; BID, twice-daily; QD, once-daily.

Table 1 – Pharmacokinetic parameters of eslicarbazepine, R-licarbazepine and oxcarbazepine following the last dose of an 8-day QD 900 mg dose of ESL or BID 450 mg dose of OXC (n=11)

	ESL 900 mg QD dose (n=11)		
	Eslicarbazepine	R-licarbazepine	Oxcarbazepine
C_{max}, µmol/L	87.3	2.7	0.8
t_{max}, h	2.5	10.1	5.3
C_{min}, µmol/L	22.7	1.8	0.2
$AUC_{\tau,0,1}$, µmol*h/L	1156.3	53.7	12.3
Fluctuation, %	131.0	41.1	128.0
Apparent terminal t½	9.1	15.0	13.2
	OXC 450 mg BID dose (n=11)		
	Eslicarbazepine	R-licarbazepine	Oxcarbazepine
C_{max}, µmol/L	48.0	9.8	4.3
t_{max}, h	3.8	3.3	1.1
C_{min}, µmol/L	31.8	5.8	0.4
$AUC_{\tau,0,1}$, µmol*h/L	968.4	188.4	31.6
Fluctuation, %	39.4	5.4	278.0
Apparent terminal t½	9.2	11.0	10.1

Notes: Results are expressed as arithmetic means; t_{max} values are median; $AUC_{\tau,0,1}$ for OXC 450 mg BID ($AUC_{\tau,0,12}$) was doubled in order to allow the comparison with the $AUC_{\tau,0,1}$ for ESL 900 mg QD ($AUC_{\tau,0,24}$); ESL, eslicarbazepine acetate; OXC, oxcarbazepine; BID, twice-daily; QD, once-daily.

RESULTS

During the course of the study, 20 treatment-emergent adverse events (TEAEs) were reported by 9 subjects in the ESL 900 mg QD group and 38 TEAEs were reported by 11 subjects in the OXC 450 mg BID group.

TEAEs considered to be possibly/definitely related to treatment and reported more than once were:

- somnolence (3 cases) and nystagmus (2 cases) in the ESL 900 mg QD group;
- somnolence (7 cases), dizziness (6 cases), frontal headache (2 cases) and nausea (2 cases) in the OXC 450 mg BID group.

As tolerability assessments are limited in healthy volunteers open-label studies of short duration and small number of subjects, these results should not be used as guidance for clinical practice.

CONCLUSION

In comparison to OXC, administration of ESL resulted in 40% increase in the efficiency to deliver eslicarbazepine, less R-licarbazepine and less oxcarbazepine, which may relate to differences in the clinical profiles of ESL and OXC.

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CONTACT INFORMATION

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Effect of eslicarbazepine acetate on plasma levels of concomitant antiepileptic drugs: a population pharmacokinetics evaluation based on double-blind phase III clinical studies

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PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures (POS), with or without secondary generalization (1).

After oral administration, ESL is extensively converted to eslicarbazepine which blocks voltage-gated sodium- and calcium-channels (1, 2).

In vitro studies revealed that eslicarbazepine may have clinically relevant effects on the activity of the cytochrome P450 isoforms CYP1A2, 2C9, 2C19, 3A4, and the uridine diphosphate-5'--glucuronosyltransferase (UGT) 1A1. The extent of possible drug-drug interactions (DDI) with antiepileptic drugs (AEDs) such as lamotrigine (LTG), topiramate (TPM), phenytoin (PHT), carbamazepine (CBZ) and valproic acid (VPA) was investigated in 4 different phase I studies and in a sub-group analysis of a phase II study, respectively.

The purpose of the current DDI analysis was to assess the potential for interactions between ESL and other AEDs in a large number of patients participating in the clinical studies, using a population pharmacokinetic (pop-PK) model.

METHODS

Blood samples for monitoring of pre-dose or steady-state trough plasma concentrations ($C_{min,ss}$) of concomitant AEDs were obtained from 641 out of 1049 patients participating in three phase III studies (Studies BIA-2093-301, -302 and -303) prior to initiation of treatment with ESL or placebo and at the end of the 12 week maintenance treatment period. A pop-PK model of eslicarbazepine, and AEDs' $C_{min,ss}$ was fitted and data were analysed using non-linear mixed-effect modelling (NONMEM) methods.

Mean end/initial $C_{min,ss}$ ratios and their 95% confidence intervals (95%CI) for the concomitant AEDs were calculated according to the treatment and the ESL dose.

As a supportive measure, plasma exposure PK parameters such as oral clearance (CL/F) and the exponential inter-individual variance of CL/F (ω^2) for each concomitant AED were calculated from individual parameters estimates derived from the model.

RESULTS

CBZ was the most frequent concomitant AED followed by VPA, LTG, TPM, phenobarbital (PB), levetiracetam (LEV), PHT, clobazam (CLB) and gabapentin (GBP) (Table 1).

No clinically relevant changes in the mean (95%CI) end/initial $C_{min,ss}$ ratios of concomitant AEDs were observed for placebo, ESL 400 mg and 800 mg QD dose groups (Figure 1 and Table 2).

In ESL 1200 mg QD treated patients, mean (95%CI) end/initial $C_{min,ss}$ ratios of CBZ, LTG and TPM were significantly reduced by 13%, 25% and 16%, respectively (Figure 1 and Table 2).

ESL increased CL/F of CBZ, LTG and TPM up to 14.2%, 12.1% and 15.8%, respectively, whereas CL/F levels of VPA, LEV, PB, PHT, CLB and GBP were not affected by concomitant use of ESL (Table 3). For CBZ and TPM, these increases demonstrated a trend of proportionality with increasing ESL dose. In the former CBZ sub-group, this effect was dependent on CBZ dose. In the LTG and TPM sub-groups, CL/F increases in patients, who additionally were taking concomitant CBZ at a median dose of 1000 and 1025 mg/day, were 5.6% and 8.5%, respectively. In this pop-PK model, ω^2 for CBZ, VPA, LTG, TPM, LEV, PB, PHT, CLB and GBP were 24.0%, 64.3%, 48.1%, 38.7%, 56.3%, 42.0%, 72.2%, 76.6% and 37.9%, respectively (Table 3).

RESULTS

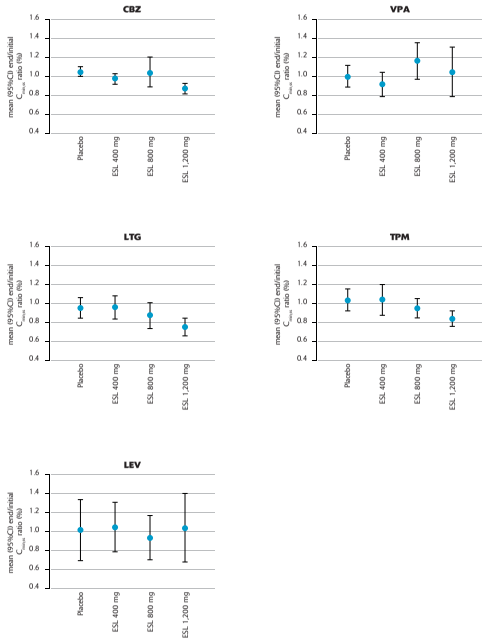

Figure 1 – Mean (95%CI) end/initial $C_{min,ss}$ ratios of AEDs used by more than 15 subjects in each treatment group by treatment and ESL dose.

Notes: CBZ, carbamazepine; CI, confidence interval; ESL, eslicarbazepine acetate; LEV, levetiracetam; LTG, lamotrigine; TPM, topiramate; VPA, valproic acid; $C_{min,ss}$, steady-state trough concentration.

Table 1 – Patients (N) with plasma level records of con-AEDs and number of records (n) by con-AED.

conAEDs	CBZ	VPA	LTG	TPM	PB	LEV	PHT	CLB	GBP
Patients (N)	256	209	203	118	93	92	81	61	31
Plasma level records (n)	1,566	675	651	370	267	272	193	124	107

Notes: con-AEDs, concomitant antiepileptic drugs; CBZ, carbamazepine; VPA, valproic acid; LTG, lamotrigine; TPM, topiramate; PB, phenobarbital; LEV, levetiracetam; PHT, phenytoin; CLB, clobazam; GBP, gabapentin.

Table 2 – Mean (95%CI) end/initial $C_{min,ss}$ ratios of AEDs used by more than 15 subjects in each treatment group by treatment and ESL dose.

conAEDs	CBZ		VPA		LTG		TPM		LEV	
end/initial $C_{min,ss}$ ratios	mean		mean		mean		mean		mean	
Treatment	n	(95%CI)	n	(95%CI)	n	(95%CI)	n	(95%CI)	n	(95%CI)
Placebo	124	1.05 (1.00, 1.10)	43	0.99 (0.88, 1.11)	41	0.95 (0.85, 1.06)	24	1.03 (0.92, 1.15)	20	1.02 (0.69, 1.34)
ESL 400 mg	96	0.98 (0.92, 1.03)	23	0.91 (0.78, 1.04)	36	0.96 (0.84, 1.08)	18	1.04 (0.88, 1.20)	21	1.05 (0.79, 1.31)
ESL 800 mg	110	1.04 (0.89, 1.20)	44	1.16 (0.97, 1.35)	39	0.87 (0.73, 1.01)	26	0.95 (0.85, 1.05)	19	0.94 (0.70, 1.17)
ESL 1,200 mg	84	0.87 (0.81, 0.93)	36	1.04 (0.78, 1.30)	34	0.75 (0.66, 0.85)	24	0.84 (0.76, 0.92)	22	1.04 (0.68, 1.40)

Notes: con-AEDs, concomitant antiepileptic drugs; $C_{min,ss}$, steady-state trough plasma concentration; ESL, eslicarbazepine acetate; CBZ, carbamazepine; VPA, valproic acid; LTG, lamotrigine; TPM, topiramate; LEV, levetiracetam; CI, confidence interval.

Table 3 – ΔCL/F and ω^2 for carbamazepine (CBZ), valproic acid (VPA), lamotrigine (LTG), topiramate (TPM), phenobarbital (PB), levetiracetam (LEV), phenytoin (PHT), clobazam (CLB) and gabapentin (GBP).

conAEDs	CBZ	VPA	LTG	TPM	PB	LEV	PHT	CLB	GBP
Δ CL/F (%)	14.2	ne	12.1*	15.8*	ne	ne	ne	ne	ne
ω^2 (%)	24.0	64.3	48.1	38.7	42.0	56.3	72.2	76.6	37.9

Notes: conAEDs, concomitant anti-epileptic drugs; ΔCL/F, percent change in oral plasma clearance; ω^2, exponential inter-individual variance on CL/F; ne, no effect; *, without CBZ effect.

CONCLUSION

This pop-PK analysis based on integrated data from three phase III clinical studies suggests that the pharmacokinetic effect of eslicarbazepine acetate on the clearance of concomitant AEDs is unlikely to be clinically relevant in most cases.

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1. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. Epilepsia 2012;53(6):935-46.
2. Gil-Nagel A, Elger C, Ben-Menachem E, Halász P, Lopes-Lima J, Gabbai AA, et al. Efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: Integrated analysis of pooled data from double-blind phase III clinical studies. Epilepsia 2012 Aug 6 [Epub ahead of print].

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Comparative bioavailability study of two different sources of eslicarbazepine acetate in healthy subjects

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PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1).

After oral administration, ESL is extensively converted to eslicarbazepine which blocks voltage-gated sodium- and calcium-channels (1, 2).

The primary objective of this study was to demonstrate the bioequivalence (BE) between two active product ingredient (API) sources of ESL: the *Reference* current API source – marketed formulation (MF) versus the *Test* new API source – to-be-marketed (TBM) formulation.

As a secondary objective the safety and tolerability of both formulations were investigated.

METHODS

This was a two-centre, open-label, randomized, gender-balanced, single-dose, laboratory-blinded, two-period, two-sequence, crossover study in two groups of 20 healthy subjects.

Subjects randomly received on period 1 and 2 either a single tablet of ESL MF or a single tablet of ESL TBM, separated by a wash-out of at least seven days between doses.

Two dosage strengths were studied – 400 mg in one group and 800 mg in the other.

One tablet was to be orally administered with 240 mL of water in the morning after a 10-hour overnight fast in each period (time of study-drug administration was to be the same for each treatment period).

For all subjects, blood samples (4 mL) were drawn for the assay of plasma ESL and its active metabolite eslicarbazepine at pre-dose and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours post-dose for each dosing period.

Safety was evaluated from clinical and laboratory assessments.

The statistical method for testing bioequivalence was based upon the 90% confidence interval (90%CI) for the ratio of the geometric means (*Test/Reference*), for the eslicarbazepine parameters under consideration ($AUC_{0,t}$, $AUC_{0,\infty}$ and C_{max}). Bioequivalence was assumed when the 90%CI for the pharmacokinetic parameters under consideration fell within the 80-125% bioequivalence range.

RESULTS

A gender balanced total of 40 healthy male and female subjects were planned and included in the study. 2 female subjects randomized to the ESL 800 mg group did not complete the study for personal reasons. 40 subjects were analysed for safety, and 38 subjects were analysed for pharmacokinetics.

ESL plasma concentration was below the limit of quantification at almost all sampling times. Therefore, pharmacokinetic analyses were performed only for the main active metabolite eslicarbazepine.

The mean eslicarbazepine plasma profiles following a single oral dose of ESL MF and ESL TBM are presented in Figure 1 for the 400 mg group and in Figure 2 for the 800 mg group.

RESULTS

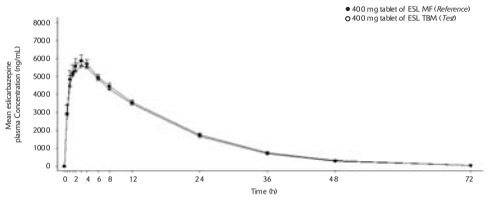

Figure 1 – Mean (+SEM) eslicarbazepine plasma profile following single 400 mg administration of ESL MF (*Reference*) and ESL TBM (*Test*) in 20 healthy subjects. Linear representation.

Notes: ESL, eslicarbazepine acetate; MF, marketed formulation; TBM, to-be-marketed formulation.

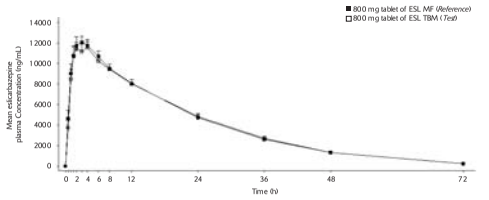

Figure 2 – Mean (+SEM) eslicarbazepine plasma profile following single 800 mg administration of ESL MF (*Reference*) and ESL TBM (*Test*) in 18 healthy subjects. Linear representation.

Notes: ESL, eslicarbazepine acetate; MF, marketed formulation; TBM, to-be-marketed formulation.

Table 1 – ANOVA results for pharmacokinetic variables C_{max}, $AUC_{0,t}$ and $AUC_{0,\infty}$ of eslicarbazepine

Dose level	Parameter (unit)	Treatment group	Geometric mean	Point estimate ratio *Test/Reference*	90% CI
400 mg	C_{max} ng/mL	ESL MF (*Reference*)	6320	1.01	[0.94; 1.09]
		ESL TBM (*Test*)	6391		
	$AUC_{0,t}$ (ng*h/mL)	ESL MF (*Reference*)	110298	0.96	[0.94; 0.98]
		ESL TBM (*Test*)	105853		
	$AUC_{0,\infty}$ (ng*h/mL)	ESL MF (*Reference*)	111129	0.96	[0.94; 0.98]
		ESL TBM (*Test*)	106622		
800 mg	C_{max} ng/mL	ESL MF (*Reference*)	12950	1.00	[0.95; 1.05]
		ESL TBM (*Test*)	12808		
	$AUC_{0,t}$ (ng*h/mL)	ESL MF (*Reference*)	273474	1.00	[0.97; 1.03]
		ESL TBM (*Test*)	272679		
	$AUC_{0,\infty}$ (ng*h/mL)	ESL MF (*Reference*)	277274	1.00	[0.97; 1.03]
		ESL TBM (*Test*)	277084		

Notes: ESL, eslicarbazepine acetate; MF, marketed formulation; TBM, to-be-marketed formulation.

Table 2 – T_{max} and Wilcoxon signed ranks test results for the comparison between *Test* and *Reference* products

Dose level	Parameter (unit)	Treatment group	Number of values	Median (min – max)	p-value
400 mg	T_{max} (h)	ESL MF (*Reference*)	20	2.00 (0.5 – 6.0)	1.0000
		ESL TBM (*Test*)	20	2.00 (0.5 – 6.0)	
800 mg	T_{max} (h)	ESL MF (*Reference*)	18	2.00 (1.0 – 4.0)	0.9504
		ESL TBM (*Test*)	18	1.75 (1.0 – 6.0)	

Notes: ESL, eslicarbazepine acetate; MF, marketed formulation; TBM, to-be-marketed formulation.

RESULTS

At the two studied dosage levels, 400 mg and 800 mg, the 90% back-transformed confidence intervals for C_{max}, $AUC_{0,t}$ and $AUC_{0,\infty}$ ratios of the *Test* (TBM) and *Reference* (MF) formulations were all contained in the bioequivalence range of 0.8-1.25 (Table 1).

Additionally, at both dose levels, no evidence of difference between *Test* and *Reference* products in t_{max} ($p>0.05$) was found (Table 2).

33 subjects presented no adverse event (AE). There was no serious AE and no important medical event. No AE required the withdrawal of a subject. 13 therapeutic-emergent adverse events (TEAEs) were reported by 7 subjects (10 TEAEs were considered possibly related to study drug). Most TEAEs (11) were of mild intensity with the exception of 2 TEAEs which were moderate in intensity. All subjects had recovered at the end of the study. No clinically relevant difference was observed in the nature, the intensity of TEAEs and their relationship with investigational medicinal product, between ESL MF and ESL TBM.

CONCLUSION

The oral formulation containing 400 mg or 800 mg of ESL from the TBM source are bioequivalent to those from the MF source for both 400 mg and 800 mg of ESL. Study treatments, whatever the dosage and formulation, were well tolerated.

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2. Gil-Nagel A, Elger C, Ben-Menachem E, Halász P, Lopes-Lima J, Gabbai AA, et al. Efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: Integrated analysis of pooled data from double-blind phase III clinical studies. Epilepsia 2012 Aug 6 [Epub ahead of print].

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Steady-state plasma and cerebrospinal fluid pharmacokinetics of eslicarbazepine acetate and oxcarbazepine in healthy volunteers

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PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily (QD) anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1).

Unlike oxcarbazepine (OXC), which is metabolized to both eslicarbazepine and (R)-licarbazepine, ESL is almost exclusively converted to eslicarbazepine. The systemic exposure to eslicarbazepine after ESL oral administration is approximately 94% of the parent dose, with minimal exposure to (R)-licarbazepine and oxcarbazepine (1).

ESL and OXC active metabolites are formed in peripheral tissues and have to cross the blood-brain barrier to exert their action in the central nervous system.

It is not fully understood how the ESL and OXC metabolites differ in their ability to cross the blood–brain barrier, whether their concentrations in the cerebrospinal fluid (CSF) correlate with their plasma concentrations, and whether eventual differences in CSF pharmacokinetics correlate with their therapeutic regimens.

The objective of this study was to evaluate the steady-state pharmacokinetics of QD ESL and twice-daily (BID) OXC and their metabolites in CSF and plasma following repeated oral administration of equivalent daily doses to healthy volunteers. Tolerability was also assessed.

METHODS

This was a single-centre, open-label, randomised, parallel-group study in healthy volunteers.

Volunteers in ESL group (n=7) received 600 mg on Days 1-3 and 1200 mg on Days 4-9, QD. Volunteers in OXC group (n=7) received 300 mg on Days 1-3 and 600 mg on Days 4-9, BID.

Plasma and CSF samples for the determination of drug concentrations were taken on day 9 from pre-dose up to the end of a dosing interval.

Safety assessments consisted of adverse events monitoring, physical examinations, vital signs measurements, 12-lead ECG recordings, and standard blood and urine clinical laboratory tests.

RESULTS

In total, 14 volunteers (7 in each group) were enrolled into the study. 12 volunteers (6 volunteers in each group; 3 men and 3 women) constituted the CSF pharmacokinetics population. All enrolled volunteers (7 in each group) were included in the safety and plasma pharmacokinetic analyses.

The plasma and CSF concentration-time profiles of eslicarbazepine, R-licarbazepine and oxcarbazepine, during a dosing interval following the last dose of a repeated-dose regimen of QD 1200 mg ESL and of BID 600 mg OXC are displayed in Figures 1 – 3. The corresponding pharmacokinetic parameters are presented in Table 1.

Concentration-time profiles and pharmacokinetic parameters could not be calculated for ESL, because its plasma and CSF levels were always below the limit of quantification.

Eslicarbazepine was the major drug entity in plasma and CSF, accounting for, respectively, 93.84% and 91.96% of total exposure in the ESL group and 78.06% and 76.42% in the OXC group (Figures 1 – 3 and Table 1).

RESULTS

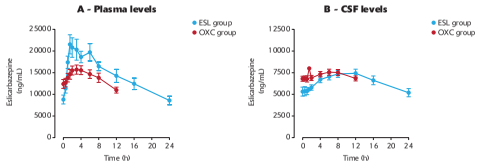

Figure 1 – Plasma (A) and cerebrospinal fluid (CSF) (B) concentration-time profiles of eslicarbazepine during a dosing interval following the last dose of a repeated-dose regimen of once-daily 1200 mg eslicarbazepine acetate (ESL) and of twice-daily 600 mg oxcarbazepine (OXC) to healthy volunteers (plasma profile: n=7 in each group; CSF profile: n=6 in each group).

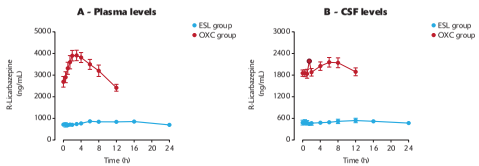

Figure 2 – Plasma (A) and cerebrospinal fluid (CSF) (B) concentration-time profiles of R-licarbazepine during a dosing interval following the last dose of a repeated-dose regimen of once-daily 1200 mg eslicarbazepine acetate (ESL) and of twice-daily 600 mg oxcarbazepine (OXC) to healthy volunteers (plasma profile: n=7 in each group; CSF profile: n=6 in each group).

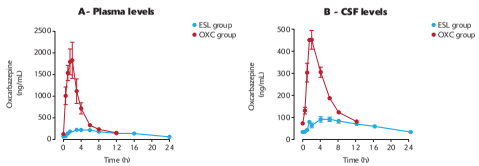

Figure 3 – Plasma (A) and cerebrospinal fluid (CSF) (B) concentration-time profiles of oxcarbazepine during a dosing interval following the last dose of a repeated-dose regimen of once-daily 1200 mg eslicarbazepine acetate (ESL) and of twice-daily 600 mg oxcarbazepine (OXC) to healthy volunteers (plasma profile: n=7 in each group; CSF profile: n=6 in each group).

Table 1 – Pharmacokinetic parameters of eslicarbazepine, R-licarbazepine and oxcarbazepine following the last dose of a repeated-dose regimen of once-daily 1200 mg ESL and twice-daily 600 mg OXC to healthy volunteers (plasma profile: n=7 in each group; CSF profile: n=6 in each group).

	ESL Group					
	Plasma (n=7)			CSF (n=6)		
	Eslicarbazepine	R-licarbazepine	Oxcarbazepine	Eslicarbazepine	R-licarbazepine	Oxcarbazepine
C_{max}, ng/mL	24698 ± 6630	911 ± 235	253 ± 73	7616 ± 1050	553 ± 145	96 ± 27
t_{max}, h	2.4 (1.0-6.0)	8.0 (0.5-16.0)	3.0 (1.0-6.0)	12.0 (6.0-16.0)	12.0 (0.5-16.0)	4.0 (4.0-12.0)
C_{min}, ng/mL	8417 ± 2696	642 ± 171	57 ± 27	5027 ± 1054	451 ± 115	31 ± 4
$AUC_{0,t}$, ng.h/mL	345962 ± 70412	19182 ± 4619	3445 ± 762	155777 ± 22495	12072 ± 2909	1543 ± 287
$AUC_{\tau,0-24h}$, ng.h/mL	345962 ± 70412	19182 ± 4619	3520 ± 679	155777 ± 22495	12072 ± 2909	1543 ± 287
Fluctuation, %	113.0 ± 33.7	33.2 ± 9.2	133.0 ± 35.2	40.6 ± 12.1	20.1 ± 5.6	99.0 ± 21.3
Fluctuation, (peak-to-trough)	2.9	1.4	4.4	1.5	1.2	3.1
$T_{1/2}$	15.9 ± 2.2	64.1± 41.7	10.7± 2.3	24.8 ± 8.1	61.8 ± 32.1	10.9 ± 0.7

	OXC Group					
	Plasma (n=7)			CSF (n=6)		
	Eslicarbazepine	R-licarbazepine	Oxcarbazepine	Eslicarbazepine	R-licarbazepine	Oxcarbazepine
C_{max}, ng/mL	16353 ± 2662	4077 ± 613	2129 ± 941	7610 ± 912	2166 ± 327	459 ± 109
t_{max}, h	3.0 (2.0-4.0)	3.0 (2.0-4.0)	1.5 (1.0-1.5)	6.0 (1.5-8.0)	6.0 (6.0-8.0)	2.0 (1.5-2.0)
C_{min}, ng/mL	10945 ± 1843	2409 ± 426	124 ± 18	6567 ± 779	1785 ± 260	72 ± 17
$AUC_{0,t}$, ng.h/mL	167160 ± 29904	39564 ± 7094	7439 ± 2561	86608 ± 9545	24201 ± 3495	2513 ± 400
$AUC_{\tau,0-12h}$, ng.h/mL	167160 ± 29904	39564 ± 7094	7439 ± 2561	86608 ± 9545	24201 ± 3495	2513 ± 400
Fluctuation, %	39.0 ± 6.4	51.1 ± 10.3	315.0 ± 43.8	14.4 ± 2.1	18.8 ± 4.0	182.0 ± 24.8
Fluctuation, (peak-to-trough)	1.5	1.7	17.2	1.2	1.2	6.4

Notes: Data are given as arithmetic mean±SD (median and range for t_{max}). T1/2 is not stated for OXC administration as the duration of sampling was limited to 12 hours.

Table 2 – Number of treatment-emergent adverse events (TEAEs) and their incidence (% of subjects with that particular AE) following a repeated-dose regimen of eslicarbazepine acetate (ESL) and oxcarbazepine (OXC).

TEAEs	ESL group		OXC group	
	Incidence n (%)	Number of events	Incidence n (%)	Number of events
Headache	2 (29%)	2	7 (100%)	13
Dizziness	3 (43%)	4	6 (86%)	12
Fatigue	2 (29%)	2	5 (71%)	9
Somnolence	1 (14%)	4	3 (43%)	7
Nausea	1 (14%)	1	5 (71%)	7
Vision blurred	0	0	3 (43%)	6
Back pain	1 (14%)	1	5 (71%)	5
Stomach discomfort	0	0	3 (43%)	5
Any TEAE*	6 (86%)	24	7 (100%)	84

Notes: The table only shows TEAEs reported by at least 3 subjects in any treatment group; *all TEAEs were included and not only the ones listed in the table.

RESULTS

The C_{max} and extent of exposure to drug entities R-licarbazepine and oxcarbazepine was approximately 4-fold higher with OXC as compared with ESL (Figures 2 – 3 and Table 1).

There was relatively little fluctuation from peak to trough (ratio) in the CSF for both eslicarbazepine (ESL = 1.5; OXC = 1.2) and R-licarbazepine (ESL = 1.2; OXC = 1.2). In contrast oxcarbazepine showed larger differences between peak and trough (ESL = 3.1; OXC = 6.4) (Figures 1 – 3 and Table 1).

A total of 84 and 24 treatment-emergent adverse events (TEAEs) were reported with OXC and ESL, respectively (Table 2). As tolerability assessments are limited in healthy volunteers open-label studies of short duration and small number of subjects, these results should not be used as guidance for clinical practice.

CONCLUSION

In comparison to OXC, administration of ESL resulted in more eslicarbazepine, less R-licarbazepine and less oxcarbazepine in plasma and CSF, which may correlate with the tolerability profile reported with ESL.

The apparent smaller peak-trough fluctuation of eslicarbazepine in CSF than in plasma support once-daily dosing of ESL.

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1. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. Epilepsia 2012;53(6):935-46.

CONTACT INFORMATION

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

A clinical study method used to evaluate the efficacy and safety of the novel antiepileptic drug eslicarbazepine acetate in children with partial-onset seizures

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[1]BIAL - Portela & Ca. SA, S. Mamede do Coronado, Portugal; [2]University of Porto, Porto, Portugal

PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily (QD) anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures (POS), with or without secondary generalization (1).

After oral administration ESL is extensively converted to eslicarbazepine which blocks voltage-gated sodium- and calcium-channels (1, 2).

Following an exploratory phase IIa study (3), this phase III, randomized, double-blind study aims to assess the efficacy and safety of ESL as adjunctive therapy in 252 children and adolescents (2 to 18 years old) with POS, not controlled with 1 or 2 antiepileptic drugs (AEDs).

METHODS

The study design is schematically represented in Figure 1.

The randomised, double-blind, placebo-controlled, parallel-group phase of this study will consist of an 8 week observational baseline period followed by a 6 week double-blind titration period, a 12 week double-blind maintenance period, a double-blind tapering-off period, and a 4 week observational follow-up period (Figure 1).

After the baseline period, patients with at least 4 seizures/4 weeks will be randomised in a ratio of 1:1 to receive double-blind treatment with ESL or placebo in addition to current concomitant therapy with 1 or 2 AEDs. The randomisation will be stratified by age group (2-6 years; 7-11 years; 12-18 years). The concomitant AED therapy must be kept stable during double-blind part of the study.

The study treatment should be administered QD, preferably at the same time of the day.

The recommended dose ("target dose") of double-blind study treatment will be 20 mg/kg/QD.

Patients aged 2–6 years will receive the study treatment as 50 mg/mL ESL or matching placebo oral suspension. Patients aged 7–18 years will receive the study treatment in the form of 200 mg ESL or matching placebo tablets.

The primary and main secondary endpoints included in this study are shown in Table 1.

Table 1. Primary and main secondary endpoints

Primary endpoint
1. Responder rate (defined as the proportion of patients with at least a 50% decrease in the standardised seizure frequency)
2. Relative reduction in the standardised seizure frequency
Secondary endpoints
• Safety and tolerability
• % of seizure-free patients
• % of patients with more than 75% reduction in seizure frequency
• Frequency of patients with exacerbations
• Duration and severity of seizures (using the Hague seizure severity scale)
• Potential for rebound effects and withdrawal phenomena
• Potential for interaction between ESL and concomitant AED medication
• Seizure frequency by seizure type
• Maintenance of the therapeutic effect of ESL during long-term treatment in OLE of the study

METHODS

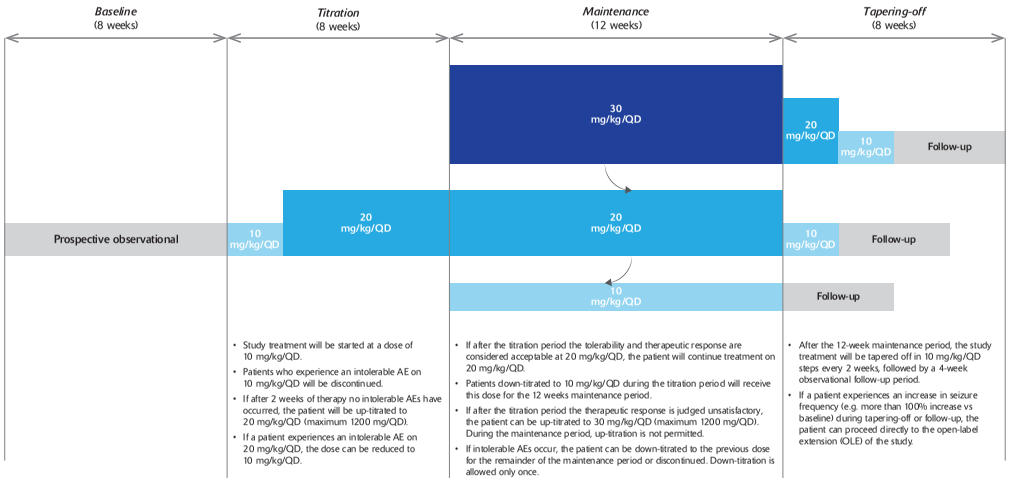

Figure 1. Study design of the double-blind phase.

Notes: Dosages refer to eslicarbazepine acetate or matching placebo tablets. AE, adverse event; QD, once-daily.

METHODS

At the end of the double-blind phase, patients will be invited to participate in an open-label extension (OLE) period with ESL. The starting dose will be 10 mg/kg/QD. The daily dose will be titrated by the investigator according to clinical response in the dose range from 10 mg/kg/QD to 30 mg/kg/QD (maximum 1200 mg/QD).

Down-titration in steps of 10 mg/kg/QD will be allowed in case of intolerable adverse events (AEs).

If a patient is treated with only 1 concomitant AED and becomes seizure-free during treatment in the OLE, the concomitant AED can be tapered off (switch to monotherapy with ESL).

RESULTS

The study is currently ongoing at 72 sites in 17 European countries and 18 sites in 4 Asian countries.

The double-blind phase is expected to be completed by the end of 2012, and the results will be reported thereafter.

CONCLUSION

This study has been designed to evaluate the risk/benefit ratio of ESL in children with POS as part of the clinical development plan of ESL.

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

Design of a phase III, double-blind, double-dummy, active-controlled, multi-national non-inferiority monotherapy study of eslicarbazepine acetate versus controlled-release carbamazepine in adults with partial-onset seizures

Moreira J[1], Trinka E[2], Mota F[1], Nunes T[1], Soares-da-Silva P[1,3]

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PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily (QD) anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures (POS), with or without secondary generalization (1).

After oral administration, ESL is extensively converted to eslicarbazepine which blocks voltage-gated sodium- and calcium-channels (1, 2).

This phase-III, randomised, double-blind, double-dummy, active-controlled, non-inferiority study aims to investigate the efficacy and safety of QD ESL as monotherapy treatment for newly diagnosed adults with POS in comparison with twice-daily (BID) controlled-release carbamazepine (CBZ-CR).

METHODS

The study design is schematically represented in Figure 1.

Newly diagnosed epilepsy patients ≥18 years of age with at least 2 well documented POS (with or without secondary generalization) in the past year and at least 1 in the last 3 months will be randomised in a 1:1 ratio to receive ESL 800 mg QD or CBZ-CR 200 mg BID (**dose level A**) during the initial **26 week evaluation period** (Figure 1).

In the event of seizure occurrence, subjects are titrated to **dose level B** of the evaluation period (ESL 1200 mg QD or CBZ-CR 400 mg BID). Should a subject have another seizure at dose level B, their assigned treatment is to be titrated to **dose level C** of the evaluation period (ESL 1600 mg QD or CBZ-CR 600 mg BID).

Subjects who remain seizure free for 26 weeks at any dose in the evaluation period will continue to receive the allocated treatment under double-blind conditions during a **26 week maintenance period** and a subsequent extension phase until the last patient terminates the maintenance period, which marks the lock of the database.

Subjects who have a seizure at dose level C during the evaluation period or at any dose during the maintenance period or the extension phase are to be discontinued from the study.

The primary and main secondary **endpoints** included in this study are shown in Table 1.

Table 1. Primary and main secondary endpoints

Primary endpoint
1. Proportion of seizure-free patients in the 26-week evaluation period at the last received dose level in the per-protocol (PP) population
Secondary endpoints
• Proportion of seizure-free patients during 1 year of treatment at the last evaluated dose
• Treatment retention time
• Changes in quality of life assessed using the quality of life in epilepsy-31 (QOLIE-31) questionnaire
• Assessment of mental and physical sedation as measured by Bond-Lader visual analogue scales (BL-VAS)
• Adverse events
• Clinical laboratory assessments, including measures of bone metabolism

900 patients will be randomized in order to have at least 360 per treatment group in the per-protocol (PP) population. The sample size was calculated to achieve a 90% power to establish non-inferiority, assuming that the proportion of seizure-free patients is 60% for both treatments and using a -12% absolute margin (20% relative).

METHODS

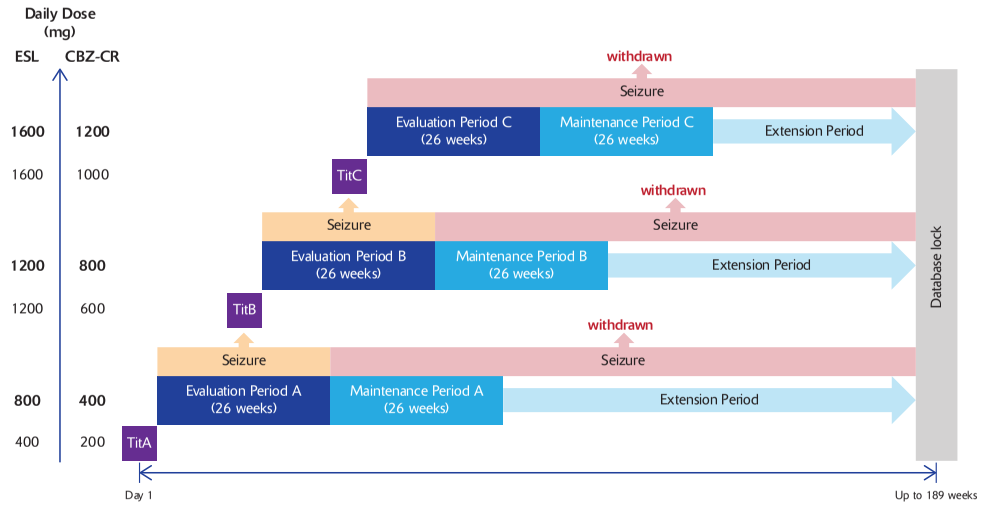

Figure 1 – Study design.

Notes: CBZ-CR, carbamazepine controlled-release; ESL, eslicarbazepine acetate; Tit, titration period. ESL is given as once-daily dosages and CBZ-CR is given as twice-daily dosage (except in the titration period A when CBZ-CR is given as 200 mg once-daily).

RESULTS

The study is currently ongoing in 170 centres in 30 countries worldwide and is expected to be completed by the end of 2013.

By showing that ESL is non-inferior to CBZ-CR, the study aims to provide evidence supporting the efficacy and tolerability of ESL as monotherapy for adults with POS.

CONCLUSION

Current European guidance indicates that the optimal study design to demonstrate efficacy of an anticonvulsant drug as monotherapy should be a non-inferiority design using stepwise fixed dose increments based on response in newly diagnosed patients.

The use of a non-inferiority design implies the pre-definition of a clinically relevant margin and adequate power to detect non-inferiority versus a gold standard.

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

Steady-state pharmacokinetics and tolerability of once-daily and twice-daily regimens of eslicarbazepine acetate in healthy volunteers

Vaz-da-Silva M[1,2], Falcão A[3,4], Nunes T[1], Almeida L[5], Soares-da-Silva P[1,2]

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PURPOSE

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalization (1).

In a phase II placebo-controlled, adjunctive therapy study in adult patients with partial-onset seizures ESL 800 and 1200 mg once-daily (QD) doses were found to be efficacious and well tolerated. However, the same doses given twice-daily (BID) were not significantly more efficacious than placebo (2).

The present study investigated the steady-state pharmacokinetics of QD and BID regimens of ESL in healthy volunteers. Tolerability was also assessed.

METHODS

This was a single centre, open-label, randomised, three-way crossover study in 12 healthy volunteers.

The study consisted of three 8-day treatment periods separated by a washout period of 10-15 days. In each treatment period the volunteers received a daily oral dose of ESL 900 mg QD, ESL 450 mg BID or oxcarbazepine (OXC) 450 mg BID (data not shown).

Blood samples for the assay of plasma ESL and its metabolites were taken at the following times in each treatment period: Day 1 to Day 7 – pre-morning dose; Day 8 – pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 and 96 h post-dose.

Safety was evaluated by monitoring of adverse events, clinical laboratory safety tests, vital signs, 12-lead ECG, and physical examinations, including brief neurological examinations.

RESULTS

Pharmacokinetic assessments were performed in 11 subjects in each of the treatment periods. Safety was assessed in all patients who had been enrolled and taken at least one dose of investigational product (n=12).

ESL plasma levels were consistently below the limit of quantification (0.17 µmol/L) at all sampling times.

The plasma concentration versus time profiles for the ESL metabolites eslicarbazepine, R-licarbazepine and oxcarbazepine over 24h, following the last dose of an 8-day QD 900 mg dose of ESL or BID 450 mg dose of ESL are shown in Figures 1 to 3.

Eslicarbazepine was the major drug entity in plasma, accounting for 94.6% and 93.9% of total exposure with ESL QD and ESL BID, respectively (Figures 1 – 3 and Table 1).

Eslicarbazepine (C_{max}) was 33% higher with ESL QD in comparison with ESL BID; $AUC_{tau,0,t}$ was 1156.3 and 1117.6 µmol*h/L, respectively (Figure 1 and Table 1).

Trough plasma eslicarbazepine before the last dose was 29.3% lower for ESL administered QD in relation to ESL administered BID (22.7 and 32.3 µmol/L, respectively).

RESULTS

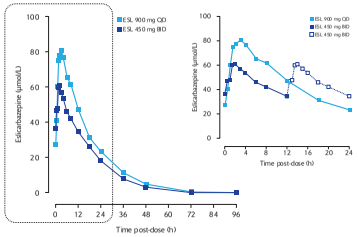

Figure 1 – Mean plasma concentration-time profile of eslicarbazepine following the last dose of an 8-day repeated dosing with ESL 900 mg QD or ESL 450 mg BID to 11 healthy subjects. The inset represents the concentration-time profile of eslicarbazepine up to 24 h following ESL 900 mg QD or ESL 450 mg BID; for ESL 450 mg BID from 12-24h (blue open squares and dotted line) is a duplication of the concentration-time profile from 0-12h as used for the calculation of $AUC_{tau,0,t}$ over a 24h period. ESL, eslicarbazepine acetate; BID, twice-daily; QD, once-daily.

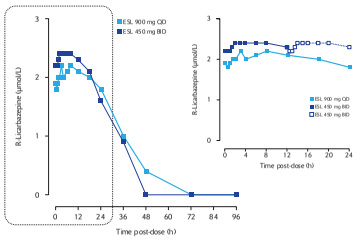

Figure 2 – Mean plasma concentration-time profile of R-licarbazepine following the last dose of an 8-day repeated dosing with ESL 900 mg QD or ESL 450 mg BID to 11 healthy subjects. The inset represents the concentration-time profile of R-licarbazepine up to 24 h following ESL 900 mg QD or ESL 450 mg BID; for ESL 450 mg BID from 12-24h (blue open squares and dotted line) is a duplication of the concentration-time profile from 0-12h as used for the calculation of $AUC_{tau,0,t}$ over a 24h period. ESL, eslicarbazepine acetate; BID, twice-daily; QD, once-daily.

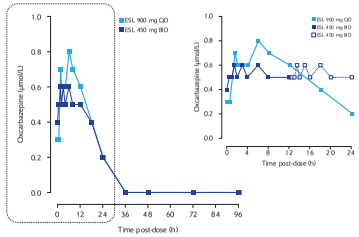

Figure 3 – Mean plasma concentration-time profile of oxcarbazepine following the last dose of an 8-day repeated dosing with ESL 900 mg QD or ESL 450 mg BID to 11 healthy subjects. The inset represents the concentration-time profile of oxcarbazepine up to 24 h following ESL 900 mg QD or ESL 450 mg BID; for ESL 450 mg BID from 12-24h (blue open squares and dotted line) is a duplication of the concentration-time profile from 0-12h as used for the calculation of $AUC_{tau,0,t}$ over a 24h period. ESL, eslicarbazepine acetate; BID, twice-daily; QD, once-daily.

Table 1 – Pharmacokinetic parameters of eslicarbazepine, R-licarbazepine and oxcarbazepine following the last dose of an 8-day QD 900 mg dose of ESL or BID 450 mg dose of ESL (n=11)

	ESL 900 mg QD dose (n=11)		
	Eslicarbazepine	R-licarbazepine	Oxcarbazepine
C_{max}, µmol/L	87.3	2.7	0.8
t_{max}, h	2.5	10.1	5.3
C_{min}, µmol/L	22.7	1.8	0.2
$AUC_{tau,0,t}$, µmol*h/L	1156.3	53.7	12.3
Fluctuation, %	131.0	41.1	128.0
Apparent terminal t½	9.1	15.0	13.2
	ESL 450 mg BID dose (n=11)		
	Eslicarbazepine	R-licarbazepine	Oxcarbazepine
C_{max}, µmol/L	65.5	2.8	0.7
t_{max}, h	2.1	6.0	4.3
C_{min}, µmol/L	32.3	2.1	0.3
$AUC_{tau,0,t}$, µmol*h/L	1117.6	59.6	13.2
Fluctuation, %	69.7	28.6	69.4
Apparent terminal t½	9.2	14.5	11.9

Notes: Results are expressed as arithmetic means; t_{max} values are median; $AUC_{tau,0,t}$ for ESL 450 mg BID ($AUC_{tau,0,t}$) was doubled in order to allow the comparison with the $AUC_{tau,0,t}$ for ESL 900 mg QD ($AUC_{tau,0,t}$); ESL, eslicarbazepine acetate; BID, twice-daily; QD, once-daily.

RESULTS

During the course of the study, 20 treatment-emergent adverse events (TEAEs) were reported by 9 subjects in the ESL 900 mg QD group and 24 TEAEs were reported by 10 subjects in the ESL 450 mg BID group.

TEAEs considered to be possibly/definitely related to treatment and reported more than once were:

- somnolence (3 cases) and nystagmus (2 cases) in the ESL 900 mg QD group;
- somnolence (3 cases) and dizziness (2 cases) in the ESL 450 mg BID group.

As tolerability assessments are limited in healthy volunteers open-label studies of short duration and small number of subjects, these results should not be used as guidance for clinical practice.

CONCLUSION

In comparison to ESL BID, administration of ESL QD resulted in 33% higher maximum concentration of eslicarbazepine with similar overall exposure, which may correlate with the efficacy profile reported with ESL.

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10th European Congress on Epileptology, London, September 30th – October 4th 2012

Annex 4 – Abstracts of three post-hoc analyses accepted as poster presentation at the forthcoming 66th American Epilepsy Society meeting, to be held in San Diego, from November 30th till December 4th 2012

Authors: António Gil-Nagel[1], Eugen Trinka[2], João Chaves[3], Edouard Hirsch[4], Rui Sousa[5], Teresa Nunes[6], Patrício Soares-da-Silva[5,6]

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Title: A post-hoc exploratory analysis of the effect of eslicarbazepine acetate as adjunctive treatment in adult patients with partial-onset seizures refractory to carbamazepine.

Rationale: Eslicarbazepine acetate (ESL) is a novel once-daily (QD) anticonvulsant, extensively converted to eslicarbazepine after oral administration, which blocks voltage-gated sodium- and calcium-channels. Although ESL and carbamazepine (CBZ) do not share any common metabolites they are chemically related. Furthermore, CBZ is one of the most frequently used antiepileptic drugs (AEDs). It is important to assess the effect of ESL in patients not achieving complete seizure control under treatment with CBZ. This *post-hoc* analysis evaluated the efficacy and tolerability of adjunctive ESL therapy in adult patients with partial-onset seizures (POS) refractory to lower and higher dosages of CBZ.

Methods: Data from two phase III multicentre, double-blind, randomized, placebo-controlled studies in adult patients with ≥4 partial-onset seizures per 4 weeks despite treatment with 1-3 AEDs was pooled and analysed. ESL was administered at QD doses of 400 mg, 800 mg and 1200 mg. Efficacy and tolerability was evaluated in patients not co-treated with CBZ (noCBZ) and patients co-treated with CBZ ≤ 800 mg daily (CBZ≤ 800) or with CBZ > 800 mg daily (CBZ>800), as part of their baseline AEDs.

Results: Safety population comprised 797 patients (noCBZ, n=328; CBZ≤ 800, n=193; CBZ>800, n=276) and intention-to treat population included 752 patients (noCBZ, n=314; CBZ≤ 800, n=183; CBZ>800, n=255). Compared with placebo seizure frequency over the 12-week maintenance period (primary end point) was significantly reduced with ESL 800 mg and 1200 mg in all three patient subgroups ($p \leq 0.05$) (table 1); ESL 400 mg was not significantly superior to placebo. Responder rate (≥50% reduction in seizure frequency) was: noCBZ group = 23% with placebo, 40% with ESL 800 mg and 39% with ESL 1200 mg; CBZ≤800 group = 18% with placebo, 37% with ESL 800 mg and 50% with ESL 1200 mg; CBZ>800 group = 16% with placebo, 31% with ESL 800 mg and 44% with ESL 1200 mg. Median relative reduction in seizure frequency was: noCBZ group = -13% with placebo, -39% with ESL 800 mg and -33% with ESL 1200 mg; CBZ≤800 group = -14% with placebo, -34% with ESL 800 mg and -50% with ESL 1200 mg; CBZ>800 group = -9% with placebo, -29% with ESL 800 mg and -38% with ESL 1200 mg. Incidence of treatment-emergent adverse events (TEAEs) was higher in CBZ>800 group (54% with placebo, 74% with ESL 800 mg and 78% with ESL 1200 mg) than in CBZ≤800 group (49% with placebo, 71% with ESL 800 mg and 71% with ESL 1200 mg) and noCBZ group (46% with placebo, 57% with ESL 800 mg and 64% with ESL 1200 mg) (table 2).

Conclusions: In this *post-hoc* analysis, the efficacy of adjunctive ESL treatment was independent from concomitant CBZ therapy. Patients with POS refractory to CBZ dosages higher than 800 mg daily achieved a significant improvement in seizure control with adjunctive once-daily ESL 800 mg and 1200 mg. The incidence of TEAEs was higher in patients treated concomitantly with CBZ, especially if CBZ dosage was higher than 800 mg daily.

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*not including authors, institutions, tables and figures

Table 1. ANCOVA of seizure frequency per 4 weeks over the 12-week maintenance period (ITT population)

Treatment	n	LS mean	SE	95% CI	p-value Comparison vs. placebo	Overall effect
No Concomitant CBZ						
Placebo	79	8.54	0.063	(7.08;10.20)		
ESL 400 mg QD	79	7.76	0.063	(6.39; 9.30)	0.7109	0.0061
ESL 800 mg QD	77	5.96	0.064	(4.78; 7.29)	0.0056	
ESL 1200 mg QD	79	6.39	0.065	(5.15; 7.80)	0.0299	
Concomitant CBZ dosage ≤800 mg						
Placebo	51	7.74	0.066	(6.29; 9.38)		
ESL 400 mg QD	45	6.94	0.071	(5.52; 8.58)	0.6892	0.0346
ESL 800 mg QD	43	5.79	0.070	(4.52; 7.24)	0.0516	
ESL 1200 mg QD	44	5.67	0.070	(4.42; 7.10)	0.0353	
Concomitant CBZ dosage >800 mg						
Placebo	68	10.12	0.071	(8.29;12.22)		
ESL 400 mg QD	68	8.89	0.073	(7.17;10.88)	0.4131	0.0015
ESL 800 mg QD	62	7.90	0.070	(6.37; 9.65)	0.0431	
ESL 1200 mg QD	57	6.72	0.070	(5.34; 8.31)	0.0005	

Notes: ANCOVA = analysis of covariance; ITT = intention-to-treat; LS = least square; SE = standard error; CI = confidence interval; n = number of patients. The ANCOVA model was based on log-transformed seizure frequencies with treatment, study, baseline seizure frequency and number of concomitant AEDs at baseline as factors. Least square means and confidence limits for the absolute effects within treatment groups have been back-transformed via the exponential function. Dunnett's multiple comparison procedure was used for the comparison of the active treatment means to the placebo mean.

Table 2. Incidence of treatment-emergent adverse events (TEAEs) in at least 10% of patients in any treatment group (safety populations).

No Concomitant CBZ				
MedDRA Preferred Term	**Placebo** (n=81)	**ESL 400 mg QD** (n=81)	**ESL 800 mg QD** (n=80)	**ESL 1200 mg QD** (n=86)
Total patients with TEAEs, n (%)	37 (45.7)	41 (50.6)	46 (57.5)	55 (64.0)
Dizziness, n (%)	5 (6.2)	3 (3.7)	10 (12.5)	12 (14.0)
Headache, n (%)	4 (4.9)	3 (3.7)	8 (10.0)	9 (10.5)
Somnolence, n (%)	5 (6.2)	11 (13.6)	8 (10.0)	17 (19.8)
Nausea, n (%)	1 (1.2)	3 (3.7)	6 (7.5)	4 (4.7)
Vomiting, n (%)	0	1 (1.2)	4 (5.0)	3 (3.5)
Diplopia, n (%)	1 (1.2)	0	2 (2.5)	5 (5.8)
Coordination abnormal, n (%)	2 (2.5)	2 (2.5)	1 (1.3)	3 (3.5)
Concomitant CBZ dosage ≤800 mg/daily				
MedDRA Preferred Term	**Placebo** (n=51)	**ESL 400 mg QD** (n=46)	**ESL 800 mg QD** (n=45)	**ESL 1200 mg QD** (n=51)
Total patients with TEAEs, n (%)	25 (49.0)	30 (65.2)	32 (71.1)	36 (70.6)
Dizziness, n (%)	1 (2.0)	6 (13.0)	10 (22.2)	11 (21.6)
Headache, n (%)	1 (2.0)	7 (15.2)	4 (8.9)	9 (17.6)
Somnolence, n (%)	6 (11.8)	3 (6.5)	6 (13.3)	8 (15.7)
Diplopia, n (%)	0	2 (4.3)	2 (4.4)	6 (11.8)
Nausea, n (%)	1 (2.0)	3 (6.5)	5 (11.1)	6 (11.8)
Vomiting, n (%)	1 (2.0)	0	2 (4.4)	4 (7.8)
Coordination abnormal, n (%)	0	1 (2.2)	1 (2.2)	2 (3.9)
Concomitant CBZ dosage >800 mg/daily				
MedDRA Preferred Term	**Placebo** (n=70)	**ESL 400 mg QD** (n=69)	**ESL 800 mg QD** (n=74)	**ESL 1200 mg QD** (n=63)
Total patients with TEAEs, n (%)	38 (54.3)	48 (69.6)	55 (74.3)	49 (77.8)
Dizziness, n (%)	6 (8.6)	17 (24.6)	24 (32.4)	34 (54.0)
Headache, n (%)	10 (14.3)	7 (10.1)	12 (16.2)	12 (19.0)
Somnolence, n (%)	8 (11.4)	7 (10.1)	12 (16.2)	6 (9.5)
Diplopia, n (%)	3 (4.3)	8 (11.6)	18 (24.3)	10 (15.9)
Nausea, n (%)	3 (4.3)	4 (5.8)	5 (6.8)	10 (15.9)
Vomiting, n (%)	3 (4.3)	3 (4.3)	9 (12.2)	7 (11.1)
Coordination abnormal, n (%)	3 (4.3)	3 (4.3)	11 (14.9)	8 (12.7)

Notes: CBZ, carbamazepine; QD, once-daily; TEAEs, therapeutic emergent adverse events. TEAEs occurring in at least 10% of patients in any treatment group are shown in bold.

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Title: A post-hoc exploratory analysis of the effect of eslicarbazepine acetate as adjunctive treatment in adult patients with partial-onset seizures and comorbid clinically relevant depressive symptoms.

Rationale: Eslicarbazepine acetate (ESL) is a novel once-daily (QD) anticonvulsant, extensively converted to eslicarbazepine after oral administration, which blocks voltage-gated sodium- and calcium-channels. Depressive disorders are common comorbidities of epilepsy and they have been associated with a poor response to antiepileptic drug therapy. This *post-hoc* analysis evaluated the efficacy and tolerability of ESL as adjunctive treatment in adult patients with partial-onset seizures (POS) and co-morbid clinically relevant depressive symptoms.

Methods: Data from two (BIA-2093-301 and -302) phase III multicentre, double-blind, randomized, placebo-controlled studies in adult patients with ≥4 partial-onset seizures per 4 weeks despite treatment with 1-3 AEDs was pooled and analysed. ESL was administered at QD doses of 400 mg, 800 mg and 1200 mg. ESL efficacy and tolerability was evaluated in subjects with and without clinically relevant depressive symptoms at baseline, as defined by Montgomery-Asberg depression rating scale score (MADRS) ≥10 and <10, respectively. MADRS score <10 have been previously shown to define remission from major depression (Affective Dis 2002; 72:177-184.)

Results: Safety population comprised 796 patients (MADRS≥10, n=325; MADRS<10, n=471) and intention-to treat population included 751 patients (MADRS≥10, n=303; MADRS<10, n=448). Compared with placebo seizure frequency over the 12-week maintenance period (primary endpoint) was significantly reduced with ESL 800 mg and 1200 mg both in patients with MADRS score ≥10 (p=0.03 and p=0.004, respectively) and with MADRS score <10 (p=0.0007 and p=0.0003, respectively) (table 1). Responder rate (≥50% reduction in seizure frequency) was: MADRS score ≥10 group = 13% with placebo, 32% with ESL 800 mg and 35% with ESL 1200 mg; MADRS score <10 group = 23% with placebo, 39% with ESL 800 mg and 49% with ESL 1200 mg. Median relative reduction in seizure frequency was: MADRS score ≥10 group = -4% with placebo, -31% with ESL 800 mg and -30% with ESL 1200 mg; MADRS score <10 group = -20% with placebo, -38% with ESL 800 mg and -48% with ESL 1200 mg. Incidence of treatment-emergent adverse events (TEAEs) was similar in MADRS score ≥10 group (55.8% with placebo, 63.4% with ESL 800 mg and 73.8% with ESL 1200 mg) and in MADRS score <10 group (45.6% with placebo, 69.2% with ESL 800 mg and 67.0% with ESL 1200 mg) (table 2).

Conclusions: In this *post-hoc* exploratory analysis, once-daily ESL 800 mg and 1200 mg adjunctive therapy was significantly superior to placebo in reducing POS in adult patients with co-morbid clinically relevant depressive symptoms. This subgroup of patients with MADRS scores ≥10 at baseline was particularly drug resistant as compared to patients without clinically

relevant depressive symptoms (MADRS scores<10) as shown by a worse seizure control either in placebo and ESL treated groups.

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*not including authors, institutions, tables and figures

Table 1. ANCOVA of seizure frequency per 4 weeks over the 12-week maintenance period (ITT population)

Treatment	n	LS mean	SE	95% CI	p-value Comparison vs. placebo	Overall effect
Baseline MADRS score <10						
Placebo	123	8.81	0.049	(7.63;10.11)		<0.0001
ESL 400 mg QD	111	8.31	0.053	(7.08; 9.67)	0.8183	
ESL 800 mg QD	107	6.42	0.053	(5.38; 7.56)	0.0007	
ESL 1200 mg QD	107	6.29	0.052	(5.29; 7.40)	0.0003	
Baseline MADRS score ≥10						
Placebo	75	8.68	0.060	(7.26;10.27)		0.0095
ESL 400 mg QD	81	7.10	0.057	(5.91; 8.43)	0.1102	
ESL 800 mg QD	75	6.68	0.058	(5.52; 7.97)	0.0306	
ESL 1200 mg QD	72	6.19	0.060	(5.07; 7.46)	0.0040	

Notes: ANCOVA = analysis of covariance; ITT = intention-to-treat; LS = least square; SE = standard error; CI = confidence interval; n = number of patients. The ANCOVA model was based on log-transformed seizure frequencies with treatment, study, baseline seizure frequency and number of concomitant AEDs at baseline as factors. Least square means and confidence limits for the absolute effects within treatment groups have been back-transformed via the exponential function. Dunnett's multiple comparison procedure was used for the comparison of the active treatment means to the placebo mean.

Table 2. Incidence of treatment-emergent adverse events (TEAEs) in at least 10% of patients in any treatment group (safety populations).

Baseline MADRS score <10				
MedDRA Preferred Term	**Placebo** (n=125)	**ESL 400 mg QD** (n=114)	**ESL 800 mg QD** (n=117)	**ESL 1200 mg QD** (n=115)
Total patients with TEAEs, n (%)	57 (45.6)	78 (68.4)	81 (69.2)	77 (67.0)
Dizziness, n (%)	6 (4.8)	16 (14.0)	30 (25.6)	33 (28.7)
Headache, n (%)	9 (7.2)	11 (9.6)	15 (12.8)	18 (15.7)
Somnolence, n (%)	13 (10.4)	11 (9.6)	17 (14.5)	15 (13.0)
Nausea, n (%)	4 (3.2)	5 (4.4)	11 (9.4)	10 (8.7)
Vomiting, n (%)	2 (1.6)	2 (1.8)	8 (6.8)	5 (4.3)
Diplopia, n (%)	3 (2.4)	7 (6.1)	16 (13.7)	8 (7.0)
Coordination abnormal, n (%)	4 (3.2)	4 (3.5)	12 (10.3)	7 (6.1)
Baseline MADRS score ≥10				
MedDRA Preferred Term	**Placebo** (n=77)	**ESL 400 mg QD** (n=82)	**ESL 800 mg QD** (n=82)	**ESL 1200 mg QD** (n=84)
Total patients with TEAEs, n (%)	43 (55.8)	41 (50.0)	52 (63.4)	62 (73.8)
Dizziness, n (%)	6 (7.8)	10 (12.2)	14 (17.1)	24 (28.6)
Headache, n (%)	6 (7.8)	6 (7.3)	9 (11.0)	12 (14.3)
Somnolence, n (%)	6 (7.8)	10 (12.2)	9 (11.0)	16 (19.0)
Nausea, n (%)	1 (1.3)	5 (6.1)	5 (6.1)	10 (11.9)
Vomiting, n (%)	2 (2.6)	2 (2.4)	7 (8.5)	9 (10.7)
Diplopia, n (%)	1 (1.3)	3 (3.7)	6 (7.3)	13 (15.5)
Coordination abnormal, n (%)	1 (1.3)	2 (2.4)	1 (1.2)	6 (7.1)

Notes: MADRS, Montgomery-Asberg Depression Rating Scale; QD, once-daily; TEAEs, therapeutic emergent adverse events.

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Title: A post-hoc analysis of the time to onset of efficacy after initiation of eslicarbazepine acetate as adjunctive therapy in adult patients with refractory partial-onset seizures.

Rationale: Eslicarbazepine acetate (ESL) is a novel once-daily (QD) anticonvulsant, extensively converted to eslicarbazepine after oral administration, which blocks voltage-gated sodium- and calcium-channels. This *post-hoc* analysis evaluated the efficacy, tolerability and time to onset of a clinically relevant reduction in seizure risk (RSR) after initiation of ESL as adjunctive therapy in adults with partial-onset seizures (POS).

Methods: Data from two (BIA-2093-301 and -302) phase III multicentre, double-blind, randomized, placebo-controlled studies in adult patients with ≥4 partial-onset seizures per 4 weeks despite treatment with 1-3 AEDs was pooled and analysed. ESL QD was administered at doses of 400 mg, 800 mg and 1200 mg. The key efficacy endpoints were seizure frequency during the 12-week maintenance phase adjusted per 4 weeks (primary endpoint), relative reduction in seizure frequency, and responder rate (≥50% reduction in seizure frequency). To evaluate time to onset of a clinically relevant effect, mean cumulated seizure frequency over time (MCF) was calculated for the entire double-blind period. From the increments in MCF, the instantaneous daily seizure rate was estimated using an Epanechnikov kernel estimator (bandwidth = 28 days). Relative hazard functions over time were derived comparing each of the 3 ESL dosage groups with placebo group. Tolerability was also assessed.

Results: Safety population comprised 797 patients (placebo, n=202; ESL 400 mg, n=196; ESL 800 mg, n=199; ESL 1200 mg, n=200) and intention-to treat population included 752 patients (placebo, n=198; ESL 400 mg, n=192; ESL 800 mg, n=182; ESL 1200 mg, n=180). Compared with placebo adjusted seizure frequency over the 12-week maintenance period was significantly reduced with ESL 800 mg and 1200 mg ($p<0.0001$ for both groups); ESL 400 mg was not significantly superior to placebo ($p=0.15$). Median relative reduction in seizure frequency was 13% with placebo and 34% and 38% with ESL 800 mg and 1200 mg, respectively. Responder rate was 19% with placebo and 36% and 43% with ESL 800 mg and 1200 mg, respectively. Including the titration period (up to 2 weeks), the onset of a clinically relevant effect (defined as 20% RSR compared with placebo) was observed in 28 days in ESL 1200 mg group and in 49 days in ESL 800 mg group. The 90% maximal effect was observed in 43 days in ESL 1200 mg group (24.5% RSR) and in 48 days in ESL 800 mg group (19.9% RSR) (figure 1). Treatment-emergent adverse events occurring in at least 10% of patients in any group were dizziness, somnolence, headache, diplopia and nausea (table 1).

Conclusions: In this post-hoc analysis, once-daily ESL 800 mg and 1200 mg was effective as adjunctive treatment of adult patients with refractory partial-onset seizures. Including the titration period, a clinically relevant reduction in seizure risk was achieved in 28 and 48 days of therapy with once-daily ESL 1200 mg and 800 mg, respectively. Both effective dosages were well tolerated.

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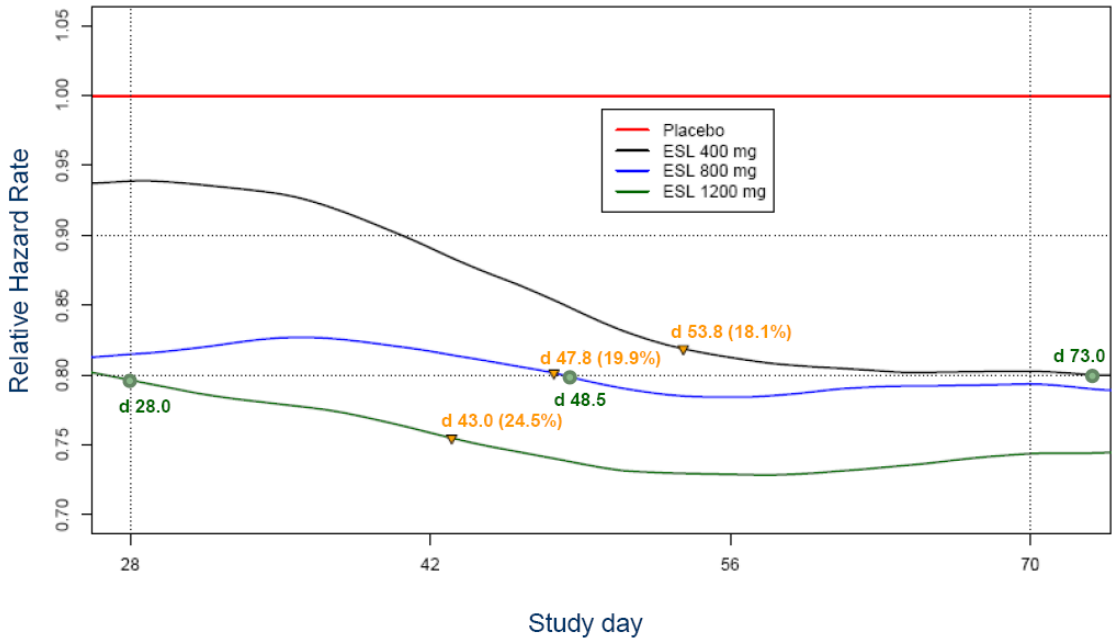

Figure 1. Relative seizure rate comparing each ESL dose with placebo. The onset of a clinically relevant effect, defined as 20% reduction in seizure risk (RSR) compared with placebo, is shown by green circles together with the estimated time (in days). The time when 90% of maximal RSR compared to placebo has been obtained is shown by orange triangles together with the estimated time (in days) and the percentage RSR.

Notes: The seizure rates were obtained using an Epanechnikov kernel estimator. A bandwidth of 28 days was chosen so the kernel estimator uses data in an interval of 28 days before and after the time of interest. This implies that the estimates in the first 28 days of therapy are influenced by baseline data and the estimates after day 70 are influenced by the data from the tapering-off period. The estimates between days 28 and 70 are not influenced by the pre-randomization or post-maintenance period so they are considered reliable.

Table 1. Incidence of treatment-emergent adverse events (TEAEs) in at least 10% of patients in any treatment group (safety populations).

MedDRA Preferred Term	**Placebo** (n=202)	**ESL 400 mg QD** (n=196)	**ESL 800 mg QD** (n=199)	**ESL 1200 mg QD** (n=200)
Total patients with TEAEs, n (%)	100 (49.5)	119 (60.7)	133 (66.8)	140 (70.0)
Dizziness, n (%)	12 (5.9)	26 (13.3)	44 (22.1)	57 (28.5)
Somnolence, n (%)	19 (9.4)	21 (10.7)	26 (13.1)	31 (15.5)
Headache, n (%)	15 (7.4)	17 (8.7)	24 (12.1)	30 (15.0)
Diplopia, n (%)	4 (2.0)	10 (5.1)	22 (11.1)	21 (10.5)
Nausea, n (%)	5 (2.5)	10 (5.1)	16 (8.0)	20 (10.0)

Notes: QD, once-daily; TEAEs, therapeutic emergent adverse events.

Annex 5 – Medical Affairs Department Award 2011

PRÉMIO SAM
2011

"Compromisso nos Desafios da Mudança"

Atribuído a
Rui Sousa

Parabéns Rui!

Por ter sido o colega da Secção dos Assuntos Médicos (SAM) que melhor se "comprometeu" com os desafios da mudança.

"Quando sopram os ventos da mudança, alguns constroem abrigos e colocam-se a salvo, outros constroem moinhos e ficam ricos" (Claus Moller).

A mudança traz variedade, traz vivacidade, dá cor à vida, implica um cortar, um repensar, um juntar de energias e um direcioná-las só para aquele ponto.

Mudar no pequeno hoje significa mudar em coisas grandes no amanhã, significa a transcendia, o sair da caixa...

Se somos o povo das descobertas, da conquista, da novidade e do vício a cheiro a novo façamos jus ao cognome.

Se nascemos para mudar, é algo que faz parte de nós... não algo que se impõe, ou que se aprende; é algo que se sente.

Um muito obrigado por ter-se 'comprometido em deixar-se desafiar para mudar'

Porto, 26 de Janeiro de 2012

Bial
ao serviço da sua Saúde